ADMINISTRATIVE INFORMATION

Title
PAD-TeGeCoach: Health Coaching and Telemetry Supported Walking Exercise for Improving Quality of Life

Roles and responsibilities
Farhad Rezvani 1, Martin Härter 1, Hans-Helmut König 2, Dirk Heider 2, Lutz Herbarth 3, Julia Brinkmann 3, Frank Bienert 3, Corinna Beutel 3, Patrick Steinisch 3, Frank Freudenstein 3, Claudia Hagenburger 3, Yvonne Große 3, Susanne Klein 4, Franziska Reif 4, Florian Kirchhoff 5, Carolin Neuschwander 5, Patrick Dickmeis 6, Thomas Heidenthal 6, Gerrit Schick 7, Barbara Koch 7, Robert Schreiber 7, Daniela Patricia Chase 7, Mark Dominik Alscher 8, Claudia Seelenmeyer 9, Jovana Radlovic 9, Jörg Dirmaier 1,

1 Department of Medical Psychology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2 Department of Health Economics and Health Services Research, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
3 KKH statutory health insurance, Hannover, Germany
4 TK statutory health insurance, Hamburg, Germany
5 mhplus statutory health insurance, Ludwigsburg, Germany
6 I.E.M. GmbH, Stolberg, Germany
7 Philips GmbH Market DACH, Hamburg, Germany
8 Robert-Bosch-Krankenhaus, Stuttgart, Germany
9 Robert Bosch Gesellschaft für medizinische Forschung mbH, Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany

a Clinical trial evaluation; b Consortial leadership and medical supervision; c Recruitment and allocation of study participants; d Implementation of telemonitoring infrastructure and technical support; e Clinical trial center

Consortial leadership
Clinical trial coordinator: Frank Bienert, KKH statutory health insurance
Address: Karl-Wiechert-Allee 61, 30625 Hannover, Germany
Telephone: +49 511 2802 3687, Email: frank.bienert@kkh.de
Medical supervisor: Dr. Lutz Herbarth, KKH statutory health insurance
Address: Karl-Wiechert-Allee 61, 30625 Hannover, Germany
Telephone: +49 511 2802 3100, Email: lutz.herbarth@kkh.de

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ABSTRACT

Peripheral artery disease (PAD) is the third most prevalent cardiovascular disease worldwide and has become a serious public health issue, with over 200 million people affected. Smoking and diabetes are the strongest risk factors for the development of peripheral artery disease, but also high cholesterol, high blood pressure and sedentary lifestyle. The most prominent symptom is leg pain while walking known as intermittent claudication, as the muscles do not get enough blood during exercise to meet the needs. To improve mobility, first line treatment for intermittent claudication are outpatient supervised exercise programs (SEPs); however, their implementation face manifold challenges: low patient adherence, no reimbursement by insurers, high costs of course implementation, and low course availability. These barriers led to the development of home-based exercise programs, which are similarly effective when combined with a structured approach by setting exercise goals, monitoring exercise activity, and regular follow up with a coach. Therefore, this trial aims to determine the clinical effectiveness and cost advantage of TeGeCoach, a 12-month long structured home-based exercise program (HEP), compared with usual care of intermittent claudication. It is hypothesized that TeGeCoach will improve walking impairment and will lower the need of health care resources that are spent on patients with PAD at 24-month follow-up.

The investigators will conduct a prospective, open-label, multicenter randomized controlled clinical trial to evaluate the effectiveness and safety of TeGeCoach. 4630 patients with peripheral artery disease at Fontaine stage II will be randomly assigned either to TeGeCoach or Treatment-as-Usual (usual care). TeGeCoach consists of telephone-based health coaching, remote walking exercise monitoring based on wearable activity monitors, and intensified primary care. The health coaching is a patient-centered approach based on motivational interviewing, shared decision-making and active listening techniques for supporting better patient engagement and activation, disease self-care, treatment adherence and lifestyle management. Depending on the individual functional status and exercise capacity, participants will be asked to walk up to seven times a week. Primary outcomes are functional capacity measured by the Walking Impairment Questionnaire, alongside with total health care costs based upon routine health insurance data. Secondary outcome measures include quality of life, health literacy and health behavior. Outcomes will be measured at three time points (0, 12, and 24 months).

Clearly, the current routine care of intermittent claudication in patients with PAD is partly ineffective and insufficient, with the consequence of a poorly served patient population and worsening disease condition. TeGeCoach may provide an effective and feasible alternative in the management of intermittent claudication by improving access to supervised exercise while at the same time potentially reducing health care costs.
INTRODUCTION

Background and rationale

Peripheral Artery Disease (PAD) is characterized by narrowing and, at later stages, occlusion of the peripheral arteries resulting in the reduction of blood supply, eventually leading to functional impairment and mobility loss. The most common etiology of PAD is atherosclerosis. PAD is the third most prevalent atherosclerotic cardiovascular disease worldwide and one of the leading causes of death, thus increasingly recognized as a serious public health concern (Creager, 2016; Criqui & Aboyans, 2015; Fowkes et al., 2013). The presence of PAD indicates a high risk for subsequent cardiovascular events and mortality; therefore, if not intervened sufficiently early, the underlying atherosclerotic processes can affect other vascular beds with potentially fatal consequences (Criqui et al., 2010).

With regard to epidemiology, the amount of people with PAD has risen in recent years (Criqui & Aboyans, 2015; Fowkes et al., 2013; Sampson et al., 2014); over 200 million people worldwide are currently affected, with a sharp increase by nearly 25% between 2000 and 2010 in the general population. This increase is disproportionally high in low- and middle-income countries (28.7%, compared to 13.1% in high-income countries) (Fowkes et al., 2013). Like all atherosclerotic diseases, PAD is markedly more prevalent in the elderly population and is rather uncommon in the younger population (Criqui & Aboyans, 2015; Fowkes et al., 2013), estimating that 5.4% and 18.6% of individuals aged between 45-49 and 85-89 years are affected by PAD, respectively (Fowkes et al., 2013). Furthermore, disability and mortality due to PAD has become a major public burden and has increased significantly in the last two decades, with a bigger increase among women than among men (Sampson et al., 2014). Likewise, in Germany, the proportion of PAD-related hospitalizations has increased from 2.7% (400 928 among 15 million hospitalizations) to 3% (483 961 among 16.2 million hospitalizations) between 2005 and 2009, particularly of last stage PAD presenting as ulcers and/or gangrene by 32% (Malyar et al., 2013). At the same time, across German hospitals, reimbursement costs for the treatment of PAD have grown from €2.14 billion in 2007 to €2.56 billion in 2009, a 21% increase within 2 years (Malyar et al., 2013). Given these findings, it is apparent that the economic burden of PAD placed on healthcare systems is high and is probably continuing to rise (Mahoney et al., 2010; Malyar et al., 2013).

A number of studies have sought to determine the association between PAD and putative risk factors (Criqui & Aboyans, 2015; Fowkes et al., 2013). In virtually all studies, former and/or current tobacco smoking has been shown to be the number one cause of PAD (Criqui & Aboyans, 2015; Eraso et al., 2014; Fowkes et al., 2017; Joosten et al., 2012), hence smoking cessation is imperative in the management of PAD leading to decreased mortality (Armstrong et al., 2014). Other patient-determined risk factors are diabetes mellitus, elevation of total cholesterol, hypertension, sedentary lifestyle, history of cardiovascular disease (i.e., coronary heart disease, stroke) and chronic kidney disorder (Criqui &
Aboyans, 2015; Fowkes et al., 2013). Recently, low socioeconomic status has also been identified as a determinant of PAD (Pande & Creager, 2014).

Although 50% of patients are asymptomatic (Hirsch et al., 2001; McDermott et al., 2001), one common clinical manifestation of PAD is leg pain while walking, known as *intermittent claudication* (IC). At an advanced stage, when PAD is fully manifesting due to the occlusion of the arteries, typical manifestations are resting leg pain, ulcer formation and gangrenous necrosis (i.e., tissue loss) due to critical limb ischemia, which, at worst case, can lead to limb loss or death (Hirsch et al., 2001). IC reflects impaired hemodynamics and vascular dysfunction (Hamburg & Creager, 2017; Hiatt, Armstrong, Larson, & Brass, 2015), although asymptomatic PAD patients may still suffer from functional impairments, regardless of limb symptoms. As IC is associated with a complex array of symptoms with diminished mental health and lower health-related quality of life, reducing them is a cornerstone of the comprehensive care for patients with PAD (Maksimovic et al., 2014; Regensteiner et al., 2008; Smolderen et al., 2009).

Debate continues about the best strategies for the management of PAD. Besides pharmacotherapy and surgical procedures, the positive effect of conservative exercise therapy in the management of PAD on pathophysiology, functional and patient-relevant outcomes (Guidon & McGee, 2010; Haas, Lloyd, Yang, & Terjung, 2012; Hamburg & Balady, 2011; Lane, Ellis, Watson, & Leng, 2014) has been recognized in a variety of international guidelines like the German guideline on the diagnosis and treatment of PAD, as well as the US and UK equivalent AHA/ACC and NICE guidelines, respectively (see Gerhard-Herman et al., 2017; Lawall, Huppert, Espinola-Klein, & Rumenapf, 2016; Lawall, Huppert, Espinola-Klein, Zemmrich, & Rümenapf, 2017; Lawall, Huppert, & Rümenapf, 2016; Layden, Michaels, Bermingham, Higgins, & Group, 2012). Accordingly, a considerable amount of controlled studies and a number of systematic reviews have been published on supervised exercise programs (SEPs) as a conservative management approach for the treatment of PAD. Based on the most current US guideline, SEPs are minimum three month commitments at least three sessions per week (30-45 minutes per session) and that are carried out in a supervised clinical setting (i.e. hospital, outpatient facility, physician’s office). For best outcomes, SEPs ideally incorporate interval training of progressive intensity until maximal claudication pain (Haas et al., 2012), thereby improving hemodynamics and modifying several other pathophysiological mechanisms (Haas et al., 2012; Hamburg & Balady, 2011). Recent evidence suggests that the successful implementation of SEPs should be the first line treatment option to target PAD, due to its compelling benefits by strengthening walking performance and markedly increasing quality of life (Fakhry et al., 2012; Kruidenier et al., 2012; Malgor et al., 2015; Parmenter, Dieberg, & Smart, 2015). SEPs are even beneficial for those patients without IC (McDermott et al., 2009), as PAD-associated functional impairments are likewise present in asymptomatic patients (McDermott et al., 2008).
Despite its merits, a major problem with SEPs as a conservative therapy approach is a lack of guideline adherence (Berger & Ladapo, 2017); in fact, in reality only a small proportion of patients participate in SEPs (Gerhard-Herman et al., 2017; Makris, Lattimer, Lavida, & Geroulakos, 2012). Against this backdrop, questions have been raised about the clinical value of SEPs in the management of PAD, as its routine care implementation remains challenging. The implementation of SEPs mainly faces threefold challenges: 1) low adherence, which is the paramount issue in the routine care of PAD, that is, many patients have been found to drop out of treatment prematurely or decline to participate (Harwood, Smith, Cayton, Broadbent, & Chetter, 2016); 2) SEPs not always feasible, because insurance companies often do not fully reimburse for SEPs and thus requiring patients to make co-payments, along with a lack of available local training centers (Layden et al., 2012); 3) high costs of course implementation for health insurance companies may be a barrier to set up new SEPs for patients with PAD (van Asselt et al., 2011). As a matter of fact, financial and organizational barriers are likely to aggravate in the future and will continue to hinder implementation of SEPs in routine care, given the increasing trend in the prevalence of classic risk factors and the ageing of the population determining higher prevalence rates.

In light of these drawbacks to SEPs, the development of alternative treatment options are of paramount importance. It is evident that the current routine care management of PAD resting upon SEPs poses a set of substantial economic and organizational challenges. Therefore, studies have emerged that offer alternative approaches to encourage PAD patients to physical exercise, thereby taking the aforementioned limitations of SEPs into account (McDermott & Polonsky, 2016). Previous studies have demonstrated that structured home-based exercise programs (HEPs) are effective and may be more feasible and accessible to patients (Collins et al., 2011; Fakhry, Spronk, de Ridder, den Hoed, & Hunink, 2011; Gardner, Parker, Montgomery, & Blevins, 2014; Gardner, Parker, Montgomery, Scott, & Blevins, 2011; McDermott & Polonsky, 2016). Unlike SEPs, HEPs take place in the personal setting of the patient.

However, as with SEPs, low adherence to HEPs still remains a major issue (Gerhard-Herman et al., 2017). This fact may account for the finding that HEPs might be less beneficial as SEPs (Al-Jundi, Madbak, Beard, Nawaz, & Tew, 2013; Fokkenrood et al., 2013; Makris et al., 2012). This implies that HEPs may still be a feasible option for PAD patients when structured like receiving an exercise regimen similar to SEPs by initially creating an exercise plan for the patient; and when measures to improve adherence are implemented. In fact, HEPs that are coupled with adherence-improving measures aiming for health behavior changes (i.e., health coaching, exercise monitoring with goal setting and regular feedback) are similarly efficacious as SEPs in the treatment of PAD (Gerhard-Herman et al., 2017). For example, a recently completed study has shown that using an activity tracker with real-time feedback, which is reviewed at follow-up visits leads to better functional and patient-reported PAD outcomes (Normahani et al., 2017). Similarly, it was shown that HEPs that are coupled with the use of an activity tracker and
exercise monitoring at regular feedback meetings results in better adherence and is efficacious in improving functional and pathophysiologicaPAD outcomes (Gardner et al., 2014; Gardner et al., 2011). These findings indicate HEPs turn out to be effective when combined with the structured approach to exercise and exercise monitoring seen in SEPs, that is, when some form of supervision-resembling measures like in SEPs are implemented (Fokkenrood et al., 2013). In contrast, unstructured exercise recommendations like simple “go home and walk” approaches are not efficacious in treating PAD (Mays, Rogers, Hiatt, & Regensteiner, 2013).

Another promising approach is combining HEPs with (telephone-based) health coaching, incorporating patient education and health-related goal setting to promote self-care by the patient. Health coaching has been shown to be a cost-efficient and effective tool in the management of diseases while inducing behavior change (Härter et al., 2016; Kivela, Elo, Kyngas, & Kaariainen, 2014). Recent evidence suggests that six months of weekly group-mediated meetings with a six month follow-up period of regular phone calls are efficacious in improving functional (McDermott et al., 2014; McDermott et al., 2013) as well as psychosocial outcomes (Rejeski et al., 2014) in patients with PAD. In a similar manner, HEPs coupled with health literacy-strengthening measures increases the amount of reported exercise (Simmons, Sinning, Pearson, & Hendrix, 2013).

Extensive research has been carried out on attrition-improving measures to successfully improve adherence to HEPs, however more high-quality trials with bigger sample sizes on how to resourcefully achieve behavioral change in patients with PAD are necessary (Galea, Weinman, White, & Bearne, 2013). Although both health coaching and exercise monitoring have been shown to improve adherence to HEPs, thereby improving functional capacity and patient-reported outcomes of PAD, uncertainty exists about their combined effect. Therefore, TeGeCoach was developed, a 12-month long telephone-based health coaching intervention with remote exercise monitoring (telemonitoring) and intensified care mediated by a regular primary care physician (PCP). Other programs incorporating remote exercise monitoring have been shown to be effective for those with coronary heart disease (e.g. Maddison et al., 2014), demonstrating the great potential and feasibility of telemonitoring.

To our knowledge, so far no other clinical trial has evaluated telephone-based health coaching with remote exercise monitoring and an intensified primary care for patients with PAD.

Objectives

Based on the currently existing gaps in the management of PAD, the present study aims to explore the empirical evidence pertaining to the effects of TeGeCoach in the management of PAD. The objective of this trial is to evaluate the clinical effectiveness and cost advantage of TeGeCoach compared with usual care of PAD (Treatment-as-Usual, TAU), focusing on two primary outcomes: 1) Walking impairment and 2) health care costs per patient. It is hypothesized that TeGeCoach would improve walking
impairment and simultaneously lower the need of health care resources that are spent on patients with PAD.

**Trial design**

This is a German, prospective, three-site, parallel group, open-label randomized controlled clinical trial (RCT), comparing routine care (control arm, TAU) with the TeGeCoach intervention (intervention arm) for patients with PAD. The home-based TeGeCoach intervention consists of telephone-based health coaching with remote exercise telemonitoring as well as intensified primary care. The length of TeGeCoach will be 12 months, followed by a period of 12 months where participants receive no health coaching anymore, but still have access to an activity tracker. Based on baseline (t0, preintervention) and two postintervention follow-up measurements at 12 months following completion of intervention (t1) and again at 24 months (t2), this trial seeks to determine whether TeGeCoach is inferior to TAU.

This clinical trial is coordinated by the KKH, a statutory health insurance company that has successfully designed and conducted clinical trials in recent years (e.g. Dwinger et al., 2013; Härter et al., 2016). This study protocol is reported in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) statement (Schulz, Altman, & Moher, 2010); the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Chan et al., 2013); and the Template for Intervention Description and Replication (TIDieR) checklist (Hoffmann et al., 2014). To control for publication bias, TeGeCoach will be registered at www.clinicaltrials.gov after being approved by the ethics committee of the Medical Association Hamburg (Landesärztekammer Hamburg). TeGeCoach is designed and conducted in full compliance with Good Clinical Practice quality standards and in accordance with the Declaration of Helsinki of 2008. It is expected that final results are reported after study completion in 2021.
Figure 1. Study overview.

**METHODS: Participants, interventions, and outcomes**

**Study setting**

TeGeCoach is a structured HEP for patients with PAD implemented in the personal setting of the patient. The telephone-based health coaching will be carried out by three different telemedicine centers located throughout Germany. Each center is affiliated to one of the three participating health insurance companies in this study (KKH, TK, mhplus) and is staffed with a specially trained medical team.
Eligibility criteria

Inpatient and outpatient diagnoses from routine statutory health insurance data will be used to identify eligible patients. TeGeCoach is indicated and for patients with IC (Fontaine stage IIa or IIa, Table 1), whereas exercise is considered to be contraindicated at advanced stages of PAD (Fontaine stage III or IV).

The study’s eligibility criteria is: between 35 and 80 years of age; insured with one of the three participating health insurance companies; sufficient German language skills to follow the telephone-based health coaching; access to a telephone (landline or mobile); and a primary or secondary diagnosis of PAD at Fontaine stage IIa or IIb within the last 36 months, corresponding to the following ICD-10-German Modified (GM) 2017 Codes: I70.21 Atherosclerosis of native arteries of extremities with IC (> 200 m, Fontaine stage IIa, Table 1); I70.22 Atherosclerosis of native arteries of extremities with IC (< 200 m, Fontaine stage IIb); I73.9 Peripheral vascular disease, unspecified (Fontaine stage IIa or IIb). However, patients should have no primary or secondary diagnosis of PAD at Fontaine stage I within the last 12 months: I70.20 Atherosclerosis of native arteries of extremities without IC (Fontaine I); and no diagnosis of Fontaine stage III or IV within the last 36 months: I70.23 Atherosclerosis of native arteries of extremities with ischemic rest pain (Fontaine III); I70.24 Atherosclerosis of native arteries of extremities with ulceration (Fontaine IV); I70.25 Atherosclerosis of native arteries of extremities with gangrene (Fontaine IV).

Ineligible patients are identified based on diagnoses that were made in inpatient settings only, given the considerable number of diagnostic errors in outpatient settings. The study’s exclusion criteria are: Immobility that goes beyond claudication (inability to carry out intervention and competing risks); severe and persistent mental disorders (adherence reasons); suicidality (safety reasons); life-threatening somatic diseases (e.g., cancer; competing risk); active or recent participation in any other PAD intervention trial; ongoing hospitalization; alcoholism and other drug dependency (adherence reasons); and heart failure graded NYHA class III and IV (inability to carry out intervention and competing risks).

### Table 1. Fontaine stages for the clinical classification of PAD.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Asymptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIa</td>
<td>Claudication at a distance &gt; 200 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIb</td>
<td>Claudication at a distance &lt; 200 m</td>
<td></td>
<td></td>
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<tr>
<td>Stage III</td>
<td>Ischemic rest pain</td>
<td></td>
<td></td>
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<tr>
<td>Stage IV</td>
<td>Ulcer, gangrene</td>
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Interventions

**TeGeCoach:** The TeGeCoach intervention is delivered over 12 months, followed by a period of 12 months during which the intervention is suspended. The central approach of the telephone-based health coaching intervention is the delivery of health information to strengthen health literacy, to facilitate patient empowerment and to adopt a proactive stance in dealing with their disease. The health coaching is a patient-centered approach based on motivational interviewing, shared decision-making as well as active listening techniques and is based on the transtheoretical model ("stages of change"). The coaching is carried out by specially trained coaches with clinical work experience.

Over the course of 12 months, patients will receive nine phone calls by their health coach. The health coaching model of TeGeCoach consists of five patient-tailored modules to the management of PAD: 1) Home-based walking exercise with telemonitoring; 2) Knowledge of PAD; 3) PAD medication; 4) PAD and important comorbidities; and 5) other related health topics (tobacco use, nutrition and vaccination). Each phone call focuses on one or more of these modules. For each module, evidence-based educational materials has been developed, which will be provided beforehand in either an electronic form or as printed output. The PCPs are constantly involved receiving regular health reports.

1) The module **home-based walking exercise with telemonitoring** is the central component of TeGeCoach. Initially, patients receive information about the walking exercise while pointing out the importance of regular exercise in PAD. Depending on the patient’s functional status and current exercise capacity, the health coach individuals exercise goals by assigning them to one out of three walking exercise prescriptions (goal setting): A: 15 minutes of walking per day; B: 15 – 30 minutes walking per day; or C: 60 minutes of walking per day. Patients will be asked to walk up to seven times a week. Upon implementation, the accompanying PCP initially reviews, and if necessary, adjusts the walking exercise plan. The PCP also checks if all important comorbidities such as high blood pressure, diabetes and coronary heart disease are sufficiently treated. The walking exercise is based on the principle of interval training; patients are asked to walk as long as claudication pain is tolerable, with rests in between. The primary objective is to gradually increase intensity as tolerated with longer periods of walking, less rest between walking sets, and, if possible, to improve overall endurance with longer exercise sessions.

To ensure the required exercise intensity and endurance to be beneficial and to facilitate exercise adherence, patients will continuously wear an activity tracker device (Beurer AS 95 Pulse; or Philips Health Watch) to review their exercise performance and for remote exercise monitoring by the health coach (telemonitoring). In a pre-study, both devices have been tested for validity. The devices continuously record the number of
steps per minute and the heart rate of the patient, which will be remotely sent to the health coach once per day via modem. This activity information will be regularly reviewed by the health coach to ensure that the patient adheres to the individual walking exercise prescription. To respond to adverse events if necessary and in order to detect problems with the walking exercise prescription, additional calls ("Intervention calls") are made when step frequency, the duration of exercise sessions, or the heart rate fall below or go above an individual threshold. During these calls, barriers like lack of motivation, exercise intolerance or technical issues will be discussed and how they can be overcome through behavioral support.

During the 12-month follow-up period of TeGeCoach, when health coaching is suspended, patients still have access to the activity tracker to review their exercise performance. There will be no remote exercise monitoring by a health coach.

2) The module Knowledge about PAD comprises information about PAD, how it develops and what the treatment options are. The objective of this module is to strengthen the patient’s health literacy.

3) The module PAD medication comprises information about the drugs prescribed for PAD. As part of the quarterly health reports, the current medication will be regularly reviewed by the accompanying PCP. The objective is to identify deviations from the clinical practice guidelines for PAD and to check whether gaps in care exist. If necessary, changes to prescribed medications will be made by the accompanying PCP.

4) The module PAD and important comorbidities comprises information about the most important comorbidities such as diabetes, hypertension, coronary heart disease and the risk for a stroke, tailored to the individual health status of the patient. The objective is to increase health literacy regarding PAD-related comorbidities. Accordingly, appropriate treatment strategies and how to reduce the risk of comorbidities in PAD are discussed.

5) The module other health topics addresses high-risk lifestyle behaviors and health issues that play a major role in PAD, tailored to the individual lifestyle of the patient. The primary goal is to encourage behavioral changes, to make lifestyle adjustments and to establish healthy habits that may help preventing a progression of their disease. If demanded, further information regarding course offers near their location and health support is offered to the patient.

Compliance of the health coaches to coaching guidelines and module is continuously monitored. Quarterly reviews will be conducted by a team of experts to assure quality in health coaching.
Routine care of PAD (TAU): Patients randomized to TAU receive written information about courses offered by their statutory health insurance. These courses are also offered to participants in the intervention group, thus retaining normal access to routine care. At Fontaine stage Ila and IIb, treatment of PAD is mainly conservative and preventive in nature. Besides antiplatelet drugs to prevent thrombosis, treatment at these stages consists of regular exercise and risk factor management. Therefore, health insurance companies offer a variety of courses to encourage regular exercise and to promote lifestyle changes, including SEPs (vascular and cardio exercise), physical therapy, nutritional assistance programs, smoking cessation programs, weight loss programs, as well as patient education programs for obesity and diabetes.

Outcomes

Outcome measures are listed in Table 2 along with timing of assessment; routine health insurance data, data collected by the health coach (coaching software) and a variety of well-established and psychometrically validated patient-reported outcomes (paper-based questionnaires) will be used to examine efficacy, safety and cost effectiveness of TeGeCoach. Primary outcomes are walking impairment, and health care costs at the 24-months follow-up measurement (t2). Treatment success of TeGeCoach is defined as significantly better walking performance as well as overall lower health care costs. Secondary outcome measures include generic and PAD-specific health-related quality of life, health status, risk factor exposure, health literacy, patient activation, use of medical services and (severe) adverse events.

Primary Outcomes:

- **Walking impairment** (Walking Impairment Questionnaire, WIQ): The patient-reported WIQ is a valid clinical tool to classify patient-perceived walking impairment in patients with PAD in terms of pain, walking speed, walking distance and the climbing of stairs (McDermott et al., 1998; Regensteiner, Steiner, Panzer, & Hiatt, 1990; Sagar, Brown, Zelt, Pickett, & Tranmer, 2012). The WIQ has been shown to be responsive to treatment effects and thus can be used as an alternative to treadmill testing for an objective assessment of walking claudication (Nicolai et al., 2009).

- **Health care costs** (routine health insurance data): hospital billing and insurance reimbursement; inpatient hospital cost; inpatient rehabilitation costs; ambulatory care costs; costs for drugs and other medical supplies; and sick pay costs. The sum of these costs will give an estimation of the total cost of treating patients with PAD.

Secondary Outcomes:
- **Generic health-related quality of life** (EQ5D-5L questionnaire): The EQ5D-5L is a standardized instrument developed by the EuroQol Group for the measurement of health-related quality of life (Herdman et al., 2011). There are five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ5D-5L has been validated for the general German population (Hinz, Kohlmann, Stöbel-Richter, Zenger, & Brähler, 2014).

- **Health status** (SF-12 questionnaire): The SF-12 is a self-report questionnaire for the measurement of generic health status involving multiple health dimensions: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. SF-12 is a short version of the SF-36, with good psychometric properties (Ware Jr, Kosinski, & Keller, 1996). The German version has been cross-validated with the original English version (Gandek et al., 1998).

- **PAD-specific health-related quality of life** (King’s College Hospital’s Vascular Quality of Life instrument, VascuQoL-25 questionnaire): The VascuQoL-25 is a highly-responsive validated questionnaire for the measurement of PAD-specific health-related quality of life (Morgan, Crayford, Murrin, & Fraser, 2001), with a high level of construct and convergence validity (Mehta, Subramaniam, Chetter, & McCollum, 2006). The questionnaire consists of five domains (Activity, Symptom, Pain, Emotional and Social) and has 25 items in total.

- **Depression** (PHQ-9 questionnaire): The PHQ-9 is a brief valid questionnaire for the diagnosis of depression (Kroenke & Spitzer, 2002; Martin, Rief, Klaiberg, & Braehler, 2006) that can also be used to identify depression outcome measures and changes over time (Löwe, Kroenke, Herzog, & Gräfe, 2004). The German version has been validated twice (Henkel et al., 2003; Lowe et al., 2004).

- **Generalized Anxiety Disorder** (GAD-7 questionnaire): The GAD-7 is brief questionnaire for the detection of Generalized Anxiety Disorder, which has been validated in primary care setting and in the general population (Lowe et al., 2008; Spitzer, Kroenke, Williams, & Löwe, 2006).

- **Risk factors** (AUDIT-C & FTND questionnaires): The AUDIT-C is a brief screening instrument to identify harmful alcohol consumption, consisting of three questions (Bradley et al., 2007; Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). Regarding its psychometric properties, the AUDIT-C has been shown to be reliable and valid instrument to screen alcohol misuse in primary care settings (Dybek et al., 2006). To identify tobacco dependence, the 6-item long Fagerström Test for Nicotine Dependence (FTND) will be used, which has been shown to be validly assessing the physical addiction to nicotine (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991).

- **Health literacy** (HLS-EU-16 questionnaire): The HLS-EU-16 is a short and comprehensive tool for the measurement of health literacy, developed by the European Health Literacy Consortium (Sørensen et al., 2013).
- **Patient activation** (PAM-13 questionnaire): PAM-13 has been shown to be a valuable tool for the measurement of patient activation by dividing people into one of four activation levels (Hibbard, Mahoney, Stockard, & Tusler, 2005). The German version has been validated, with good psychometric properties (Brenk-Franz et al., 2013; Zill et al., 2013).

- **Use of medical services** (routine health insurance data): time period until hospitalization; probability of hospitalization; number and duration of inpatient hospitalization; outpatient medical treatment; drug dose (defined daily dose - DDD)

- **Severe (adverse) events** (routine health insurance data): death, amputation, revascularization, etc.

Additional secondary outcomes will be measured in the intervention arm only. However, these outcomes cannot be used to analyze the effectiveness of TeGeCoach:

- **Fontaine stage** (coaching software data): The Fontaine classification is a clinical classification method which has been shown to be a useful tool for research purposes. There are five Fontaine stages (Table 1), from asymptomatic to major tissue loss.

- **Patient satisfaction** (ZAPA questionnaire): ZAPA is a brief (4 items) and psychometrically valid German questionnaire for measuring the patient’s global satisfaction with his or her outpatient care, including the quality and extent of information received and his/her involvement in clinical decisions (i.e. shared-decision making) (Scholl et al., 2011).

- **Walking exercise adherence** (ad-hoc items, e.g. amount of low adherence-triggered calls)

- **Amount of steps** (coaching software data): Beurer AS 95 Pulse.

**Sample size**

We aim to provide unambiguous results while minimizing the effects of random errors, hence we plan to have a large sample size and high statistical power to detect treatment effects of TeGeCoach with the highest probability possible. In line with the available health coaching resources, we will recruit 4630 patients (2 315 per group) to this clinical trial. At an estimated drop-out rate of 70% (intervention arm) and 80% (study arm) (see Dwinger et al., 2013; Härter et al., 2016; Härter et al., 2013), there would be 695 and 463 participants in the two study arms at t2, respectively. This target sample size will provide a power of 93% (Gpower v.3.1.9.2) to detect small effects (Cohen’s f = 0.10) between the two study arms with a type 1 error rate of 5%, which is substantially higher than the usual power of 80%. However, we seek to keep the beta error as low as possible to determine actual differences between both study arms at the highest probability possible.
Table 2. Participant timeline: Time schedule of enrolment (eligibility screen, informed consent, pseudonymization and allocation), study arms (TeGeCoach or TAU) and measurements (questionnaires and routine health insurance data).

<table>
<thead>
<tr>
<th>Time point *1</th>
<th>Study period</th>
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<tbody>
<tr>
<td></td>
<td>Enrollment</td>
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**Enrollment**
- Eligibility screen (routine health insurance data)
- Informed consent
- Pseudonymization
- Allocation

**Study arms**
- TeGeCoach
- TAU

**Measurements**

**intervention and control arm**
- Patient-reported outcomes (questionnaires) *2
- Cost-effectiveness and medical outcomes (routine health insurance data) *3

**Control arm only**
- Patient-reported outcomes (questionnaires) *4
- PAD severity (coaching software) *5
- Walking exercise parameters (activity tracker) *6

*1 -t1: ~1 month before patient in, t0: baseline; t1: 12 month follow-up t2: 24 month follow-up

*2 WIQ, EQ5D-5L, SF-12, VascuQoL-25, AUDIT-C, Fagerström test, HLS-EU-16, PAM-13

*3 Health care costs, use of medical services, (severe) adverse events

*4 ZAPA, ad hoc-items (low adherence-triggered calls)

*5 Fontaine stage

*6 Amount of steps per day, heart rate

Recruitment

Patients: Potentially eligible patients with PAD are recruited nationwide by three statutory health insurance companies: KKH, TK and mhplus. Based on routine health insurance data, these three health insurance companies prospectively identified approximately 36,189 eligible patients. Across successive phases of recruitment, these patients will be contacted by phone to get more detailed information about the study, to inform them about the personal benefits of participation, independent of being allocated to the intervention or control arm; and by mail, receiving a study recruitment information package. This package will include: 1) an informed consent form consisting of the patient information sheet, explaining the purpose, possible benefits and risks of the study, and the consent certificate; 2) a privacy policy statement; and 3) a consent form to exchange medical information to recruit the PCP and to allow the PCP and the health coach to share important medical information. The order of the recruitment process (phone call, then mail, or vice versa) varies across the three statutory health insurance companies, in accordance with their internal policies for recruitment. Potential participants will be asked to sign and
send back the informed consent form if they want to participate in the study. Non-responders and patients that are still interested in the study, but have not given written consent yet, will be followed up once or twice via telephone. No participant will be recruited without full, written informed consent. The intended recruitment period is expected to last 6 months and will be stopped when enough eligible participants have been enrolled to the study.

The cost effectiveness of TeGeCoach will be determined based on routine health insurance data. Only those participants that are enrolled in the clinical trial and randomized to one of the study arms are included in the analysis. Correspondingly, it is not planned to analyze the routine data of all eligible participants, but only from those who are actually participating in the study.

PCPs (intervention arm): Participants may elect his/her preferred PCP. If a PCP refuses to participate, the patient will be referred to a nearby PCP that participates in the study throughout the duration of TeGeCoach. The participating health insurance companies use open-house contracts allowing PCPs to join the contract by offering a reimbursement for his additional medical services during the study. Negotiation is limited as the terms of the contracts are fixed. Once enrolled, the health coach will contact the PCP to discuss the course of the intervention (including the issuance and confirmation of the individual walking exercise plan).

METHODS: Allocation of TeGeCoach

Sequence generation

After being enrolled to the study (written consent received), participants will be allocated in a 1:1 ratio to either the intervention (TeGeCoach) or routine care arms (TAU), stratified by health coaching site (i.e. telemedicine centers).

Allocation concealment

Once the written consent have been received by the recruitment staff, a query is submitted to the data coordinator of the respective health insurance company, which assigns a pseudonym to the patient. In order to prevent selection bias and to eliminate any predictability, randomization will be executed by the online randomization tool www.sealedenvelope.com, a secure internet-based randomization service including concealment, stratification and blocking for each health coaching site, and which allocates the patient either to TeGeCoach or TAU.

Blinding

Given the nature of the study there can be no blinding of the health coaches, PCPs, or patients. However, blinding of the outcome assessors will be implemented, so that the assessors will not have access to information about the actual study arm behind the allocation until the end of the analysis (assessor and analysis blinding).
METHODS: Data collection, management, and analysis

Data collection methods
Two different data sources will be addressed, using questionnaire data of the participants and routinely collected data by the health insurances for billing of claims. The routine data contains information on all contacts with the health care system (including ICD-10 codes; operations and procedure key code—OPS, the German equivalent to the American procedure coding system—PCS); medication; and inability to work. The three health insurance companies assemble and pseudonymize the routine data.

Once enrolled, to ensure confidentiality, the data coordinators of the three health insurance companies will assign a pseudonym to the potential participant, which transforms the name into a unique patient identification number. All data will be analyzed and stored in a pseudonymized form.

Questionnaire data: Shortly after being allocated to one of the two study arms at t0 (baseline), the data coordinators sent out a set of paper-based questionnaires to the participants, which will be sent back to the Department of Medical Psychology at the University Medical Center Hamburg-Eppendorf, responsible for the scientific evaluation of this clinical trial. At each measurement time point, the pseudonym of the participant is noted on the questionnaires in order to merge them into a longitudinal dataset for later statistical analysis. At each measurement time point (t0, t1, t2), the Department of Medical Psychology sends out a list of pseudonyms from which questionnaires were returned to the data coordinators of the health insurances. Through these lists, the data coordinators know which participants should receive a reminder for sending back the respective questionnaire. The patients will be reminded once. All participants will be followed up at t1 and t2, regardless of whether questionnaires have been returned at previous study points.

Routine data: In accordance with German data transparency regulations, aggregated pseudonymized routine health insurance data from the participants will be made available by the three participating statutory health insurance companies to the University Medical Center Hamburg-Eppendorf for research purposes. Individual insurance information cannot be identified from this data.

Data management
Data management and storage will be carried out in accordance with the data protection regulations and Good Scientific Practice recommendations by the German Research Foundation (Deutsche Forschungsgemeinschaft, 2013). Questionnaire data will be entered into an electronic database at the Department of Medical Psychology at the University Medical Center Hamburg-Eppendorf. Data management and primary data analysis will only take place at the University Medical Center Hamburg-Eppendorf. All computers for processing and analyzing the data are encrypted and password protected. Only authorized personnel will be allowed to retrieve, enter or change data.
Quality of data will be evaluated by monitoring the data regarding out-of-range values, illogical entries, invalid responses, and data entry checks. Missing values will be analyzed and appropriate imputation strategies will be applied.

Regarding data security, the data from questionnaires and routine health insurance data are entered and kept in a paper data storage and in digital form at the Department of Medical Psychology and Department of Health Economics and Health Services Research, University Medical Center Hamburg-Eppendorf, respectively. Pseudonymized data will be treated with strict privacy, will not be passed on to any third party and will be stored for 10 years. The participant’s name never appears in connection with this data as only de-identified (i.e. pseudonymized) data will be collected. The personal data of the patients (consent forms), as well as the pseudonymization key linking the individual with their pseudonym are only accessible to the data coordinators of the health insurances. The pseudonymization key is destroyed two years after study completion, so that virtually from this point anonymization of all data has been achieved. Regarding dissemination, all publicly available data will always be fully anonymized as most journals require open access to primary data.

All participants have the right to be informed about their data, thus they can turn to the staff at the Department of Medical Psychology who will initiate all further steps. If a participant quits the study prematurely, the data already collected may be used, unless requesting their deletion. Deletion of the data cannot be requested if the data has already been anonymized. If the patients revokes the informed consent, any data already collected from that participant will be deleted.

**Statistical analysis**

*Outcomes*

**Questionnaire data:** For the primary and secondary outcome measures, descriptive (absolute and relative frequency; mean and standard deviation; median and interquartile range) and inferential statistical analyzes will be carried out to detect differences between the baseline (t0) and follow-up measurements (t1; t2). Differences between TeGeCoach and TAU are determined by means of mixed model analyses. As the telephone-based health coaching will be carried out by three different sites (i.e., telemedicine centers), this will be included as a random effect to the model in order to take potential cluster effects into account. Primarily, in order to avoid attrition bias, it is planned to carry out an intention-to-treat analysis. That is, all participants who are enrolled and are originally allocated after randomization to one of the study arms are included in the analysis, irrespective of whether or to what extent they have actually received the intervention (TeGeCoach or TAU). To allow intention-to-treat analyses, missing observations are estimated with the multiple imputation method. Studies have shown that multiple imputation is a statistically valid technique for analyzing incomplete data sets (Rubin, 2004). With regard to the questionnaire data, there is only one primary endpoint, as the cost
effectiveness information will be provided by routine health insurance data and secondary endpoints will be interpreted in an explorative manner; hence, adjusting for multiple testing is not required (Bender, Lange, & Ziegler, 2007).

**Routine data:** The differences between the two study arms will be compared both descriptively and with inferential statistics. Any imbalance at baseline (t0) between groups despite randomization will be addressed with the use of *entropy balancing*, a suitable and novel matching method. Entropy balancing allows a better balancing compared to conventional processes such as *propensity matching*. Balancing is performed using all cost parameters from the routine data (see 3.2) obtained at baseline (t0). Subsequently, the weighting variables obtained by the entropy balancing are used in random-effects regression models. In these models, the difference between the two study arms are analyzed longitudinally (t0-t2). Any differences still present to t0, even after balancing, are treated by using the Difference in differences (DID) method. The calculation by means of DiD, the relative improvement (or deterioration) of TeGeCoach compared to TAU, is achieved by inserting an interaction term between the variables study time and study arms into the regression model.

**Additional analyses (sensitivity analyses)**

Per-protocol and subgroup analyses will be carried out. Per-protocol analysis merely takes the data of those participants who have received a minimum of intervention into account (for example, at least two telephone calls, doctor's link, at least one month tracking; exact criteria will be established before the trial begins), with the aim to check robustness of the results of the intention-to-treat analysis. If the results are similar, this indicates the robustness of the results. If not, possible causes for those differences will be examined. Regarding subgroup analyses, both study arms will be analyzed at baseline (t0) in terms of health insurance affiliation (KKH + mhplus vs TK), as well as the degree of walking impairment (WIQ: low vs. high).

**METHODS: Monitoring**

**Data monitoring**

This trial does not require monitoring by a formal data monitoring committee (DMC) or any performance of interim analyses as the safety concerns in this clinical trial are low. Participants are not at an elevated risk of severe outcomes and there are no known risks of the intervention to be tested. TeGeCoach consists of low-threshold intervention elements such as health coaching and exercise monitoring, which separately have been shown to be effective in treating PAD (e.g. Gardner et al., 2014; McDermott et al., 2013; Normahani et al., 2017).

Other quality assurance measures include: initial training of the health coaches; regular supervision of the health coaches; and internal auditing initiatives to monitor health coaching procedures and
compliance to coaching guidelines. When questions arise, patients have the opportunity to contact their health coach or their PCP.

Harms

TeGeCoach is a low risk, non-invasive intervention, and participants are medically supervised by their PCP. There are no identifiable risks pertaining to the TeGeCoach intervention. Patients allocated to TeGeCoach will have regular access to the routine care of PAD. It seems therefore unlikely that the trial has to stop due to safety reasons. However, participant safety will be monitored by recording (serious) adverse events reported during the regular coaching session. Consequently, although unlikely, (serious) adverse events can be detected at an early stage and appropriate countermeasures can be taken in a timely manner. Adverse events (AE) and serious adverse events (SAE) will be defined according to Good Clinical Practice (GCP) guidelines (Therapeutic Goods Administration, 2006). Relevant AEs can be any unfavorable disease, whether it is considered to be study-related or not. Relevant SAE can be any medical occurrence which results in death, requires inpatient hospitalization or prolongation of existing hospitalization, results in permanent or significant disability or is life threatening. Adverse events will be collected after entry into the study, while serious adverse event (SAE) will be reported to the ethics committee of the Medical Association Hamburg as an SAE.

ETHICS AND DISSEMINATION

This study protocol and the informed consent forms will be reviewed and approved by the ethical review bodies (Medical Association Hamburg) with respect to scientific content and compliance with applicable research and human subjects regulations. After obtaining approval, the ethics committee will be informed in case of any amendments made to the study protocol or informed consent forms.

Dissemination of the results of this study will occur through various channels. Results will be disseminated widely through peer-reviewed manuscripts published at leading journals in the field, reports to the funding body, international conference presentations and media press releases. Additionally, we will make the results of the study available to all insurance bodies who are interested in implementing such an intervention into routine clinical care of PAD. We also realize the value of open science and feel committed to information exchange through data being accessible to the research community to ensure a complete understanding of the effectiveness of TeGeCoach; therefore, in an attempt to tackle the problem of hidden clinical trial data, comprehensive trial data from our work will be made available (upon request) to the public and the medical research community.

DISCUSSION
The global burden of PAD requires substantial health-care resources to be expended. As the number of individuals living with PAD has increased over time so has the cost of continued PAD care, while the growing aging population will inevitably let the cost keep on rising. At the same time, the current routine care of PAD is ineffective and insufficient, with the consequence of a poorly served patient population, worsening disease condition and high mortality rates.

Patients with PAD and health care providers are increasingly interested in applying adherence-improving intervention measures to tackle the suboptimal treatment outcomes seen in SEPs and HEPs; therefore, the purpose of this clinical trial is to determine whether the combined use of a telephone-based health coaching and telemonitoring might be a feasible option for patients with PAD, thereby evaluating the efficacy and safety of the novel TeGeCoach intervention with various key elements involved; namely, a comprehensive telephone-based health coaching, supervising of exercise activity through telemonitoring; and an intensified primary care by an accompanying PCP. We expect that TeGeCoach will lead to an improvement of the patient’s health status, that is, reduced claudication with better overall mobility; increased quality of life; and better cost effectiveness compared to the current routine care of PAD.

Although similarly comprehensive interventions have been shown to be effective in treating PAD (REF), novel approaches that can be applied with smaller effort are necessary. To our knowledge no other clinical trial exists addressing the potential of combined telephone-based health coaching and remote telemonitoring specifically for the treatment of PAD. Feedback-enabled activity trackers may on the one hand improve self-management by making the patient more aware of his/her walking exercise behavior, while remote supervision from a health coach on the other hand allows regular feedback on the performed walking activity and motivational empowerment if necessary (e.g., when personal walking exercise goal has not been reached).

This study has several strengths. A hallmark of this clinical trial in the intervention group is the recruitment through different health insurance companies; the use of three different telemedicine centers that conduct the telephone-based health coaching with telemonitoring; and various PCPs supervising the patients. The clear advantage of this multidimensional multisite approach is the generalizability of the results to the real-life health care environment, along with a heterogeneous sample of representing patients with PAD ensuring high external validity. Furthermore, the large sample size in this study ensures adequate statistical power to obtain valid results despite high outcome variability. Moreover, the long follow-up period of 12 months after ending the intervention allows measuring long-term effects of the TeGeCoach intervention. If successful, the TeGeCoach intervention may be feasible for widespread adoption by routine care.

However, some limitations to this clinical trial exist. Despite extensive quality control and routine oversight to standardize procedures across telemedicine centers, we cannot fully rule out variability...
across health coaching sites, which may potentially limit the internal validity of this clinical trial. However, this will be addressed with a strict randomization process and stratification by health coaching site (i.e. telemedicine centers). Furthermore, due to the complex nature of the TeGeCoach intervention, it is difficult to determine to which aspect of the intervention the participants actually responds to (“mechanisms of impact”). However, to better understand complex pathways or to identify unexpected mechanisms, comprehensive subgroup analyses of patients allocated to the intervention arm will be carried out. Moreover, data used for health economic analysis are generated as routine data for billing of claims, which means that these data can suffer from inaccuracies or that important variables may be missing.
REFERENCES


