Design and rationale for the PREVAIL study: Effect of e-Health individually tailored encouragements to physical exercise on aerobic fitness among adolescents with congenital heart disease—a randomized clinical trial

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Intensive exercise may be an important part of rehabilitation in patients with congenital heart disease (CHD). However, performing regular physical exercise is challenging for many adolescent patients. Consequently, effective exercise encouragements may be needed. Little is known on the effect of e-Health encouragements on physical fitness, physical activity, and health-related quality of life in adolescents.

This trial is a nationwide interactive e-Health rehabilitation study lasting 1 year, centered on interactive use of mobile phone and Internet technology. We hypothesize that e-Health encouragements and interactive monitoring of intensive exercise for 1 year can improve physical fitness, physical activity, and health-related quality of life.

Two hundred sixteen adolescents (age, 13-16 years) with surgically corrected complex CHD but without significant hemodynamic residual defects and no restrictions to participate in physical activity are in the process of being enrolled by invitation after informed consent.

Physical fitness is measured as the maximal oxygen uptake (VO_2) at baseline and after 12 months by an assessor blinded to the randomization group. After baseline testing, the patients are 1:1 randomized to an intervention group or a control group.

Individually fully automated tailored e-Health encouragements—SMS, Internet, and mobile applications—aimed at increasing physical activity are delivered to the participants in the intervention group once a week. The Bandura's Social Cognitive Theory inspires the behavioral theoretical background. The e-Health intervention and the Godfrey cycle ergometer protocol have been feasibility tested and seem applicable to adolescents with CHD. The trial is expected to contribute with new knowledge regarding how physical activity in adolescents with CHD can be increased and, possibly, comorbidity be reduced. (Am Heart J 2012;163:549-56.)

Background

The impact of cardiovascular disease is of great concern worldwide because 0.5% to 2% of the adult population is affected. The burden of disability is substantial, and the prognosis may be poor.[1] This goes along with adding a significant economical burden to the health care system.

Over the last 20 years, there has been a growing population of adults with congenital heart disease (CHD).[2] The prognosis for morbidity and mortality for this group is unknown because only a minority of the patients have reached the age of 50 years.[3] Congenital heart disease is the most frequent subgroup of congenital malformations with a prevalence of 7.9 of 1000 live births in Denmark.[4] Within the next decade, 25 000 people in Denmark will live with CHD.[4] Despite improved outcome in terms of survival, systemic hypertension and atherosclerotic disease add to the increased risk for heart failure and compound their problems.[5] Together with ongoing medical problems, the patients experience feelings of being different, which has an impact on the patients health-related quality of life on a daily basis.[6]

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The overall aim of treatment and care for children with CHD is to provide them with the opportunity to live as normally and satisfactory as possible, compared with their healthy peers.[7] Among the general population, higher levels of physical activity are associated with better mental health and reduced risk of obesity and other metabolic and cardiovascular diseases.[8]

A systematic review of the existing evidence base was undertaken by searching the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and Science Citation Index Expanded until January 2, 2010. This review revealed 23 studies and no reports of randomized clinical trials testing the hypothesis that long-term encouragements to exercise can improve physical fitness in patients with CHD. Protocols and outcome measures for exercise testing and training of patients with CHD were scrutinized for development of the study.

The level of physical activity and fitness in adolescents with complex CHD compared with healthy children is significantly impaired.[9,10] This is probably lifestyle related because patients with CHD have the similar potential to improve their physical fitness by physical activity as their healthy peers.[11] Performing regular physical exercise is challenging for children and adolescents with CHD, and encouragements to an active lifestyle are needed.[12-14]

To develop a lifestyle behavior intervention to improve physical activity and physical fitness, exercise training programs in children and adolescents with CHD have been tested since 1981.[15] Selection bias has compromised the results of the studies, and only a few interventions had an impact on V_{O_2}-peak.[16] None of the studies focused specifically on the change of long-term health behavior, and no studies had self-efficacy in relation to physical activity as an issue. The optimal study and design of pediatric rehabilitation programs does not exist.[16] Further investigations are needed to elucidate the most effective rehabilitation strategies for adolescents with CHD.

Mobile phones and Internet-based programs are increasingly used in self-management interventions and are potential tools for enhancing physical activity among adolescents with CHD. Significant changes in physical activity have been demonstrated in a similar randomized trial with e-mail support including 124 healthy adolescents with a mean age of 14.1 ± 0.8 years.[17] A systematic review of technology-based interventions for promoting changes in physical activity in children and adolescents found that 7 of 9 studies indicated positive and significant changes in at least 1 psychosocial or behavioral physical activity outcome.[18] The use of a behavior change theory was associated with enhanced intervention efficacy.[18]

This trial introduces an e-Health rehabilitation program lasting 1 year, centered on the interactive use of mobile phone and Web-based technology. Bandura's Social Cognitive Theory, including the concept of self-efficacy, guided the development of the intervention.[19]

We hypothesize that mobile phone and Web-based encouragements to increase physical activity, as well as interactive monitoring of physical activity for 1 year, can improve physical fitness, physical activity, and quality of life.

Table I. Feasibility test baseline data

	Minimum	Maximum	Mean ± 1 SD
Age (y)	12.7	14.2	13.5 ± 0.6
Height (cm)	153.5	176.0	162.8 ± 7.8
Weight (kg)	47.0	55.7	50.7 ± 3.2
BMI (kg/m^2)	17.6	20.0	19.1 ± 1.0
V_{O_2} (mL/min)	2000.0	2855.0	2469.3 ± 345.7
V_{CO_2} (mL/min)	2087.0	3161.0	2717.0 ± 423.6
V_{O_2} ($mL\ kg^{-1}\ min^{-1}$)	41.2	55.4	48.8 ± 5.2
RER	1.1	1.2	1.2 ± 0.0
AT (mL/min)	0.6	0.7	0.7 ± 0.1
Load (W)	150.0	225.0	179.2 ± 29.2
HR (beats/min)	182.0	196.0	188.8 ± 5.1
FEV_1 (% predicted)	85	97	91 ± 5.2
FEV_1 (L)	2,4	3,4	2,8 ± 0,4

BMI indicates Body mass index; V_{CO_2}, carbon dioxide production; *RER*, respiratory exchange ratio; *AT*, anaerobic threshold; *HR*, heart rate; FEV_1, forced expiratory volume in 1 second.

Trial design

The trial is a randomized clinical trial. Eligible participants are randomized in a 1:1 allocation ratio to 1 of 2 arms: an intervention arm, in which the participants receive individually tailored encouragements to increase physical activity via their mobile phones in addition to the control intervention defined below, and a control arm, in which they receive the control intervention only. The trial conforms to the CONSORT criteria for research on e-Health interventions recommended by Baker et al.[20]

The e-Health program has been feasibility tested. Sign-on procedures and Web site was adapted according to evaluation. One healthy adolescent and 6 adolescents with CHD tested the feasibility of the exercise test protocol and repeated the test after 6 weeks. The participants with CHD could, without any problems, complete the baseline tests with excellent reproducibility: intraclass correlation coefficient 0.99 (Table I, feasibility test baseline data).

Participants

The patients with CHD included in this trial are adolescents with repaired heart lesions in need of lifelong medical follow-up. Patients 13 to 16 years of age from the University Hospitals in Skejby and Rigshospitalet in Denmark with repaired complex CHD, truncus arteriosus communis, transposition of the great arteries,

double-outlet right ventricle (including Taussig-Bing anomaly), congenital corrected transposition of the great arteries, atrioventricular septal defect, tetralogy of Fallot, Ebstein anomaly, subvalvular aortic stenosis, supravalvular aortic stenosis, and coarctation of aorta without clinical important residual defect are in the process of being enrolled by invitation. All patients are permitted to participate in competitive sports and have no restrictions to physical activity.

Patients are excluded if they have been diagnosed as having a syndrome or a developmental disability, experience arrhythmia or have a device implanted (pacemaker, biventricular pacemaker, or intracardiac defibrillator), and have clinical signs of heart failure or other major illnesses. Furthermore, forced expiratory volume in 1 second <80% of expected, or systolic blood pressure >150 mm Hg measured on the right arm at the day of testing, leads to exclusion.

Interventions

Participants in the control and experimental groups receive 1 hour of health education before randomization. In addition, the experimental group receives e-Health encouragements throughout the 1-year interventional period.

Control intervention

All patients in the trial will receive health education. This includes 1 group counseling session before baseline testing, mainly focusing on physical activity and, to a less extent, also dealing with smoking, alcohol, diet, and sleep. A session lasts 1 hour and comprises 3 to 5 peers of the same sex. Goal setting, peer teaching, and problem-solving support are the techniques applied. The pedagogical framework for health education is inspired by Bandura's social cognitive approach for promotion of self-efficacy.[19] Self-efficacy, rather than severity of the disease, is the most influential factor in determining whether adolescents will engage in sports or other physical activities.[21]

Experimental intervention

A 52-week Internet, mobile application, and SMS-based program provides individually tailored encouragements to physical exercise. To individually tailor the intervention in relation to physical capacity, the following question is asked when signing up for the e-Health program: how do you assess your fitness? The question is to be answered on a 5-point Likert scale from "Very Good" to "Very Poor." According to the reply, challenges are posed on beginner's level, middle level, or experienced level. The goal of the program is to have individuals participate in intense physical exercise in line with the current recommendations for healthy adolescents.[22]

The participants are approached by a new challenge every week: for example, "The challenge this week is that you must run the longest trip you've ever run. Try to see how long you can keep yourself going." The participants add the number of minutes and type of exercise to a mobile application and register the results on a personal home page (http://www.minpuls.nu/). Educational materials and tracking and simulation tools are available. The participant only has access to the personalized Web page. The program consists of 3 main approaches: health education, tailored interactive text encouragements, and a personal exercise-planning tool.

The choice of the components is sought to adhere to adolescents' lifestyle preferences concerning individuality, control, and competition.[23]

A private software deliverer (Mobile Fitness, Copenhagen, Denmark) is responsible for the portal and has developed the software tool called *MinPuls.nu*, in collaboration with the coordinating investigator and a group of stakeholders: a patient focus group and an expert panel comprising specialized nurses in cardiac adolescent medicine, specialist physiotherapist in pediatric cardiology, and specialists in exercise physiology. The title MinPuls.nu refers to *Me*, I am an adolescent—my *Pulse* must come up, so I can experience well being *now* (MyPulse.now).

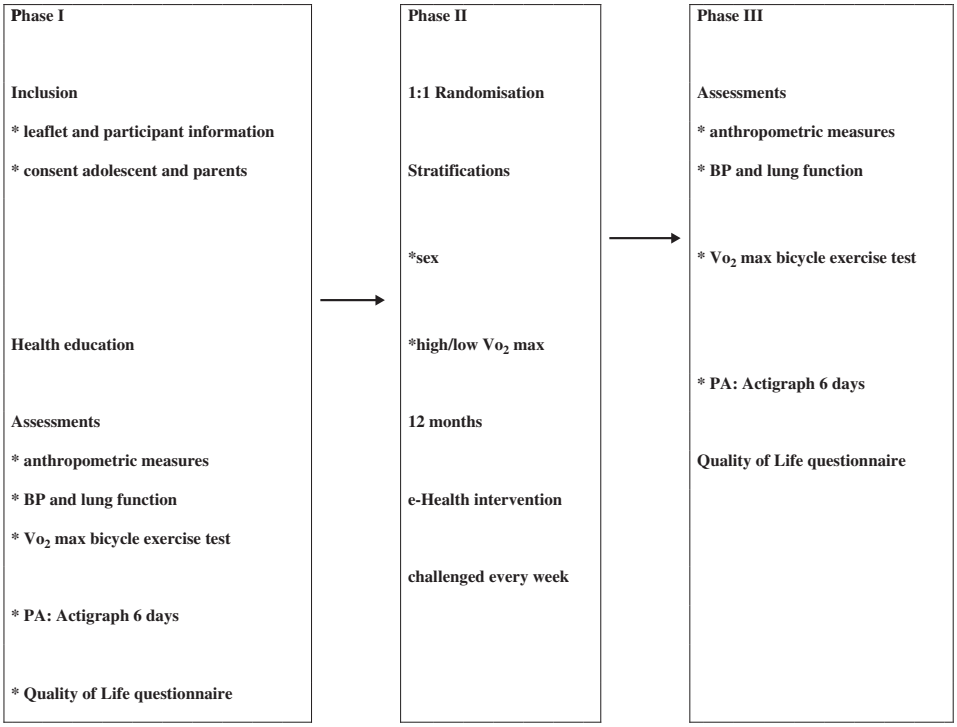
When assigned to the intervention group, the patient's and the parent's telephone numbers and e-mail addresses, as well as the patient's trial registration number, are given to the software developer. The software developer is thereafter responsible for the communications concerning the rehabilitation program with the patients and their parents during the following year (Figure 1, study phases).

Primary outcome

The primary outcome is aerobic fitness measured via Vo_2-peak with a 12-month interval. Peak Vo_2 has been found to be an independent predictor of death and/or hospitalization in patients with complex CHD.[24,25] Aerobic fitness is assessed as the maximal Vo_2 rate normalized to bodyweight (Vo_2-peak) during an incremental load test using an electronically braked ergometer cycle (Monark 839 Ergomedic, Proterapi, Brøndby, Denmark). Oxygen uptake, carbon dioxide elimination, and ventilation volume per time are measured with a computerized breath-by-breath analyzer (Master Screen CPX; Care Fusion, San Diego, CA).

After a 10-minute warm-up, the patient undergoes the Godfrey cycle ergometer protocol to elicit a maximal Vo_2 response. With the aim to complete the test within 8 to 12 minutes, the boys are starting at 25 W and increase 25 W every minute, and the girls start at 20 W and increase 20 W every minute as described by Takken et al.[26] The criterion for ending the test is patient exhaustion or if the patient develops exercise-induced

Figure 1



Study phases. BP indicates blood pressure; Vo_2 max, maximal Vo_2; PA, physical activity.

physiological signs or complaints that warrant a termination of the test. Clinical criteria for terminating the test are as follows[26]:

- Symptoms: chest pain, severe headache, dizziness, chills, sustained nausea, or inappropriate dyspnea.
- Signs: sustained pallor, clammy skin, disorientation, or inappropriate affect.
- Patient's requests for termination of the test.

The tests takes place in a well-ventilated exercise laboratory >23 m^2 at the Institute of Sports Medicine at University Hospital Bispebjerg in Copenhagen by an experienced exercise physiologist skilled in interpretation of exercise tests.[26] Achievement of maximal Vo_2 is evaluated by the following criteria: a respiratory exchange ratio of ≥1.1 to 1.2 and heart rate near maximum. Furthermore, attainment of a plateau in Vo_2 despite an increase in workload is desirable.

Secondary outcome

The secondary outcome is physical activity. Physical activity is assessed using the GTIM Accelerometer (Actigraph model 77146, Pensacola, FL), which measures the vertical acceleration of the body movement. Physical activity is monitored for 6 consecutive days immediately after the baseline tests and immediately before the outcome test: 2 weekend days and 4 weekdays. The criteria for a successful recording are a minimum of 3 days of 10 hours recording per day. Days with more than 10 hours of recordings but with periods where the accelerometer is not worn will be adjusted to a full day of 14 hours (estimated awake time for this population).[8] The participants are asked to carry the accelerometer on the left hip from the morning until going to bed, beginning the day after the baseline testing as well as 6 consecutive days after the final testing. Data will be compared with comparator cases from studies using an identical protocol. A post-stamped return envelope and written and verbal instructions are given to the child and their parents. The Actigraph is a reliable and valid tool to measure activity in adolescents.[8] The main derived physical activity parameter is the mean accelerometer counts per minute over the period of measurement.

The adolescents' self-rated physical activity is assessed by questions related to time, frequency, and intensity of physical activity as well as sedentary activities. Furthermore, self-efficacy related to exercise is analyzed.

Tertiary outcome

The tertiary outcome is health-related quality of life. Health-related quality of life is investigated using the Danish version of the Paediatric Quality of Life Inventory (Mapi, Lyon, France) for teens (ages 13-18 years), a generic module that assesses 4 domains of quality of life (physical functioning, emotional functioning, social functioning, and school functioning). The disease-specific module, which assesses 6 domains of quality of life (heart problems and treatment, treatment II, perceived physical appearance, treatment anxiety, cognitive problems, and communication), was translated and linguistically validated by 6 age-matched patients and 12 healthy adolescents according to guidelines.[27]

Adherence to the program is assessed by numbers of log-ins and use of applications (time, type, frequency, and intensity of registered physical activities). System failures and changes made to the Web site are accounted for. Type of assistance offered to sign-up procedure is recorded.

Anthropometric data

Height is measured without shoes to the nearest 0.5 cm. Weight is measured in light clothing to the nearest 0.1 kg using Tanita Fat Weight Scale BF-300 GS (Frederiksberg Vægtfabrik, Frederiksberg C, Denmark). Body mass index is calculated and evaluated as of Danish reference values.[22] Waist circumference is measured midway between the lower rib margin and the iliac crest with a nonflexible tape. Hip circumference is measured as the maximum circumference over the buttocks, with the measuring tape in a horizontal line. Body surface area is calculated ad modem Mostellar: body surface area (m^2) = (height [cm] × weight [kg]/3600). Skinfold thickness is measured with Harpenden Skinfold Caliper (Proterapi, Brøndby, Denmark) at 4 sites: the biceps, triceps, subscapular, and suprailiac sites. Calculation of body fat percentage from skin folds is performed according to Slaughter et al.[28] Blood pressure is measured on the right arm using Med Microlife BP A100 Plus (Microlife AG 9443, Widnau, Switzerland). A North Coast Hydraulic Dynamometer (Procare, Roskilde, Denmark) measures hand-grip strength, and the highest of 3 values is recorded.[29] Before exertion, a spirometric measurement is performed to assess the patients' forced vital capacity and forced expired volume in 1 second according to guidelines by SpiroUSB (Intramedic, Gentofte, Denmark). Standard equations (European Community for Coal and Steel) were used to generate the predicted values for the baseline spirometric parameters.[30]

Sample size calculation

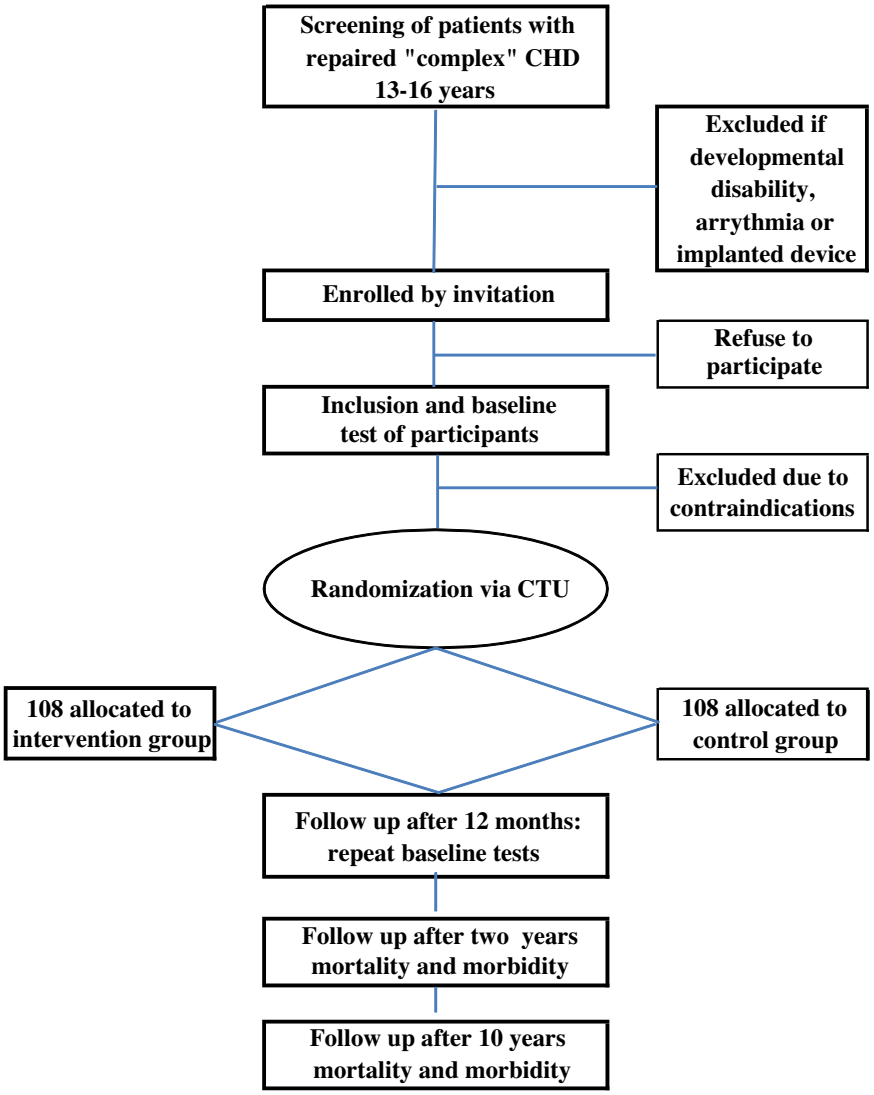
Sample size is determined and guided by previous research with adolescents with CHD. Assuming that the difference between the intervention group and the control groups in change in Watt max test from baseline to 12-month follow-up will amount to 13 W with a standard deviation of 34 W, as stated by Rhodes et al,[11] 108 are to be randomized to the experimental group. This means that we will be able to detect or refute an effect of the intervention in a randomized comparison at the size of the before- and after-difference measured in the group who carried out an exercise period in the study of Rhodes et al, assuming that the control group' Watt max does not change. The calculation is performed assuming normal distribution for the change for 1 year in the Watt max test. To detect or reject a 14% (13/93) improvement in Watt max test with a risk of type I error (α) of 5% and a risk of type II error (β) of 20% (power = $1 - \beta$ = 80%), 108 × 2 = 216 adolescents with CHD have to be included in the trial. For normally distributed data, a 2-way analysis of covariance will be undertaken on effect parameters (Group × Time), and for data, which do not fulfil the assumption of the parametric method after an appropriate logarithmic transformation, a Friedman test will be used (2-way analysis of variance). A multiple regression analysis of the change from baseline in the exercise test as a function of baseline variables will be made. It is to be analyzed if sex and self-rated health are significant predictors of the outcome. All data will be analyzed according to the intention-to-treat principle, and an unadjusted analysis as well as an analysis adjusted for design variables, including stratification variables, will be presented and discussed. A blinded statistician with no knowledge of the group allocation undertakes all statistical analysis. Primarily, the group of researchers will interpret the results, and the main conclusions of the trial are made before the de-masking of the group allocation takes place (Figure 2, flowchart).

Ethical considerations

The Danish Data Protection Agency (2007-58-0015) and the Regional Ethics Committee approved the trial protocol (H-1-2010-025), which qualified for registration in the ClinicalTrials.gov, number identifier: NCT01189981.

The rationale for providing health education as a standard intervention is, first and foremost, due to ethics reasons with reference to the Helsinki Declaration as well as the Convention on the Rights of the Child (United Nations International Children's Emergency Fund 1989), saying that patients participating in research should not provide data for the sake of the research project but gain personal benefits.[26,27] Second, the health education serves as a kickoff for individual planning of physical activity in the following year—with or without motivational support by the intervention program MinPuls.nu.

Figure 2



Flowchart. CHD indicates congenital heart defect; CTU, Copenhagen Trial Unit.

Informed consent

A cardiologist from one of the specialist centers evaluates all the eligible participants before contact. A letter from the research team, containing leaflet and participant information, is sent to all eligible participants. A follow-up telephone call is performed 10 days after the letter has been sent to the family, and the parents and the adolescent are given a verbal description of the trial. A supplementary letter is sent in case the family does not reply or cannot be reached by telephone. The participants and their parents must give their written informed consent before the adolescent can participate in the trial.

Randomization

The centralized randomization takes place 10 days after the baseline test, when the Actigraph data have been collected. We use concealed allocation and adequate computer-generated allocation sequence to avoid selection bias. Thus, neither investigators and patients nor parents can influence which groups the

patients are allocated to. The patients are randomized using the stratification variables high/low Vo_2 level at baseline and sex, to ensure balanced representation of participants with these prognostic variables in each group. Copenhagen Trial Unit undertakes the randomization using central telephone randomization.[31]

Strata is as follows: girls and boys and high/low Vo_2 peak: high Vo_2-peak girls >35.9 mL min^{-1} kg^{-1} and high Vo_2-peak boys >45.9 mL min^{-1} kg^{-1}. High/low values were determined based on research with Scandinavian adolescents with CHD in a similar age category.[9]

Allocation to the trial began in October 2010 and is planned to stop October 2012. Data collection ends October 2013, and results are expected after October 2014. A 2- and 10-year follow-up on mortality and morbidity will take place by register studies.

The trial is expected to contribute with new knowledge regarding whether physical activity improves health and, if so, how physical activity can be increased and possibly comorbidity reduced in adolescents with CHD.

Conclusion

A randomized clinical trial is undertaken to test whether a 1-year Internet, mobile application, and SMS-based program to encourage increased exercise results in better aerobic fitness. The chosen method seems applicable and feasible to adolescents with CHD. The trial is expected to contribute with new knowledge regarding whether physical activity in participants with CHD can be increased and, possibly, comorbidity be reduced.

Disclosures

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Conflict of interest: None declared. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

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