Randomized controlled clinical trial comparing adherence between two phase III cardiac rehabilitation exercise programmes – Exergame pilot study

(Research)

Jorge Ruivo, MD
Kay Karim, Nurse
Roisin O'Shea, PT
Louis Keary, MD
John Gormley, PT

(Gatekeeper)

Claire O'Brien, MD

Randomized controlled clinical trial comparing adherence between two different phase III cardiac rehabilitation exercise programmes – exergame pilot study

Background: Cardiovascular disease is the leading cause of death in developed countries. Cardiac rehabilitation should be offered to the majority of these patients, and it has been shown to improve quality of life and decrease morbi-mortality. Despite its benefits, a significant proportion of the patients still fail to comply. Research in exergaming (particularly the Nintendo Wii platform) has already shown promise in facilitating increasing physical activity and behavioral change. Wii's capacity for providing enhanced motivation levels might result in significantly raised CR attendance numbers, and a more effective healthy lifestyle behavioral change.
Design: A two arms, single-center, investigator-blinded, pilot block randomized controlled clinical trial will be conducted to compare a standard cardiac rehabilitation phase III exercise program to a Wii-supplemented exercise program. Eligible subjects include 40-75 years old patients admitted in the hospital in the past 6 months for a cardiovascular condition, with low-moderate cardiac rehabilitation risk as defined by ACSM guidelines, and no previous CR programme attendance, contraindications to exercise, or conditions that may hinder the engagement of electronic exercise platforms. After informed consentment, thirty two consecutive patients will be recruited from the partner CR referral center, at the enrollment stage. Primary outcome will be by compliance, as defined by the attendance rate at the end of the program (6 weeks), otherwise with no medical contraindication. Secondary physiological, psychological and clinical outcomes will be assessed at 6 and 14th weeks. We hypothesize that a Wii supplemented exercise regime will improve patient compliance, by positively modulating physio and psychological parameters.
The trial will be registered after Ethics Committee approval. There is no funding source or other support to disclaim.

1. Introduction

1.1 Background

Cardiovascular disease (CVD) is the leading cause of death in Europe, being responsible for 1.9 million deaths per year[1]. Mortality from CVD has decreased in developed countries in recent decades due to improved diagnosis and treatment. An increased number of people survive cardiac events, leading to an increase of the chronic morbidity burden[2].
Cardiac rehabilitation (CR) should be offered to people with certain CVD conditions[3].
In patients with coronary artery disease (CAD) it has been shown to improve quality of life and decrease subsequent morbi-mortality[3]. CR programmes achieve this through exercise, behavioral change, counseling and strategies aimed at targeting traditional risk factors for CAD. Systematic reviews show 20% reduction in users´ all-cause mortality and 27% reduction in cardiac mortality at two to five years with this approach[4]. More attendance also influences outcome, with CR users with 25 or more sessions 19% relatively less likely to die over 5 years than matched CR users with fewer sessions[5].
Despite its benefits, a significant proportion of the included patients fail to comply with the early post-discharge (phase III) programme. Investigation of CR adherence from European wide survey studies suggests that exercise rehabilitation programmes have at best an 85% compliance rate[6], depending on the country setting. Nevertheless, cardiac rehabilitation completion is particularly high in Ireland, with 68% attending at least one half of the sessions, substantially higher than the European figure of 34%[7]. The main reason for discontinuing exercise training is the lack of motivation[8]. In Ireland, those who do not complete the programme usually also claim minor illnesses, followed by readmission to hospital, exercise programme unsuitable for their needs, family reasons or return to work[9]. Such reasons reveal outstanding misconceptions that strongly influence patients' non-completion of programmes. Reduced adherence is even more frequent among ethnic minorities, female gender, older age, depressed mood, rural area living, and also in with lower physical activity, annual income, level of education and social support [4, 10, 11]. Therefore, the CR national strategy

should aim to better the compliance among these groups. More disappointingly, it is reported that less than 50% of people who participate in cardiac rehabilitation programmes maintain an exercise regimen for as long as six months after completion[10].
Exergaming seems promising in effectively increasing physical activity[12] and behavioral change towards an overall healthier lifestyle[13]. Integrating exergames in centre-based CR routine may play a role in improving adherence rates and sustaining post-discharge exercise habits, since it can also be done at home. This new generation of active-play video-games allows the person to interact with the game by performing intricate skilled exercise movements that contribute to physical fitness. The average physiological response and metabolic values attained during Nintendo Wii™ boxing (i.e. minute ventilation, oxygen uptake, heart rate, energy expenditure, fat and carbohydrate oxidation and respiratory exchange ratio) can be equivalent to those achieved during treadmill walking[14]. In addition, Wii's capacity for providing enhanced motivation levels[15] might result in significantly raised compliance numbers, contributing to further morbi-mortality decrease.

1.2 Study objective

After conducting an extensive literature review on exergaming in health, we aim to investigate the differential contribution of two different exercise protocols during CR phase III and its impact on adherence rate, by performing a randomized controlled study. We hypothesize that a Wii supplemented exercise regime will improve patient compliance, by positively modulating physio and psychological parameters.
We propose a pilot study as part of our research strategy, since a variety of factors should be resolved *a priori*, such as: a) the determination of most clinically relevant primary outcome measures (e.g. compliance, enjoyment, quality of life, exercise capacity), their reliability and feasibility of its measurement; b) the determination of the initial data for the primary outcome measure, in order to calculate the sample size for a larger trial; c) assessing the appropriateness of the level of intervention (e.g how much Wii supplementation); d) analyzing inclusion/exclusion criteria adequateness; e) estimating participation rates; e) detecting a floor or ceiling effect or f) identifying possible side-effects of the intervention (e.g., falls, tendinitis, traumatic lesions).
Furthermore, it will help to put in place certain logistical procedures, such as the storage and testing of equipment; training of staff and analyzing protocol time-consumption; estimating resource requirements; testing patient information documents and consent forms.

2. Methods

2.1 Trial design

A single center, evaluator blinded, intention-to-treat, pilot block randomized controlled trial will be pursued at Kerry General Hospital. Study protocol will be approved by the local UCC Ethics Committee and Trinity University.

2.2 Participants

The following eligibility criteria will be considered by the CR programme coordinator before invitation:

Inclusion criteria:

- Low to moderate risk CR participants, as defined by ACSM[16], 40-75 years old, admitted in the hospital in the past 6 months for a cardiovascular condition (acute coronary syndrome, stable angina, valvular disease submitted to intervention, CABG, PCI, pacemaker insertion)

Exclusion criteria:

- Previous CR programme attendance

- Present contraindication to exercise, such as unstable angina, resting SBP>200 mmHg or resting DBP>110mmHg, uncontrolled arrhythmia, decompensated heart failure, critical aortic stenosis, orthostatic blood drop >20 mmHg with symptoms, active pericarditis or myocarditis, recent embolism, thrombophlebitis or uncontrolled diabetes

- High cardiac rehabilitation risk as defined by ACSM guidelines[16], (presence of angina or -like symptoms at exertion<5 METs or recovery; presence of complex ventricular dysrythmias during exercise testing and recovery; chronotropic incompetence, decreasing SBP during exercise testing; severe postexercise hypotension; ST segment depression >=2 mm during ET or recovery; resting ejection fraction <40%; history of cardiac arrest or sudden death; complex dysrhythmias at rest; Congestive heart failure; ischemia; clinical depression

- Conditions that may hinder the engagement of electronic exercise platforms, such as learning disability, blindness, impaired balance or severe orthopaedic condition

- History of epilepsy (due to risk of seizure from video games and flashing lights), in accordance with the Nintendo manufacturer's safety precautions.

After eligibility check, subjects will be voluntarily recruited from the partner CR referral center, at the enrollment stage (sampling). An information leaflet and expression of interest form will be given by the CR programme coordinator to all eligible patients, since the Principal investigator, which is not part of the partner hospital staff, is currently based abroad, due to clinical obligations. There will be no sort of payment for participation.

Patients will be ensured that they will receive the best standard of CR care quality, irrespective of enrolling in the research study or not, thus minimizing any potential conflict of interests with programme coordinator. To ensure such standards, a local hospital higher hierarchy Consultant Physician will be appointed the project gatekeeper. The information leaflet will provide information on the study and contact details for the programme coordinator and the study supervisor, should the potential participants have any questions in relation to the study during the reflexion period (7 days). After assent to the pilot study, on the first day of baseline testing, the protocol will be explained once more and the opportunity to ask questions provided, this time around by the attending cardiologist. Subject's participation in the trial will be noted in their medical records and a copy of the signed consent form will be inserted inserted.

Demographics characterization by age, sex, ethnicity, employment status, prior Wii experience, body mass index, use of secondary prevention drugs, major modifiable risk factors (diabetes, smoking status, blood pressure, physical inactivity and lipid profile), will be performed by the CR programme coordinator, by either direct inquiry or by case notes access. This characterization, except Wii previous experience, is considered standard care.
Further baseline data on exercise capacity (submaximal exercise stress test, METs), physical activity

engagement (accelerometry) and enjoyment (PANAS Scale), anxiety and depression (HAD scale) and quality of life (MacNew questionnaire) will be collected for all patients by their attending cardiologists. Except for exercise capacity, important for exercise prescription, these data will not be available for the CR programme coordinator.

Integrating these active entertainment audiovisual tools in centre-based CR routine contributes to physical fitness, and may play a role in improving adherence rates and sustaining post-discharge exercise habits, since it can also be done at home. Injuries from engaging such audiovisual tools are very rare, characteristically mild, and usually only arise from very intense repeated exposure. Nonetheless, the risks are no greater than in the conventional rehabilitation. Moreover, volunteers will be supervised by the research team at all times throughout the experimental protocol. The study will take place in the grounds of the partnership Hospital so in the event of an adverse outcome, emergency services can be accessed promptly.

A definitive future study with adequate sample size will use new set of patients.

2.3 Interventions

Patients will originally consent to be enrolled in a study research involving supervised ambulatory exercise regime for 6 weeks, with audiovisual add-on platforms during classes, whose detailed description they are unaware of before randomization. Special attention will be given not to disclose information about both exercise protocols, not to misplace hope towards a specific group, otherwise this could generate frustration, decreased adherence afterwards, or even reduced uptake.
After randomization (Chapter 2.6), participants will either be allocated to a) a conventional exercise group (controls) in line with European guidelines[17], consisting of standard aerobic, force and flexibility training (9 conventional circuit stations) (Fig1), with audiovisual add-ons such as videomusic DVDs, or to b) a group of Wii supplemented exercise (7 conventional stations plus 2 Nintendo Wii gaming station, and a Wii 1x1 warming-up system) (Fig1).

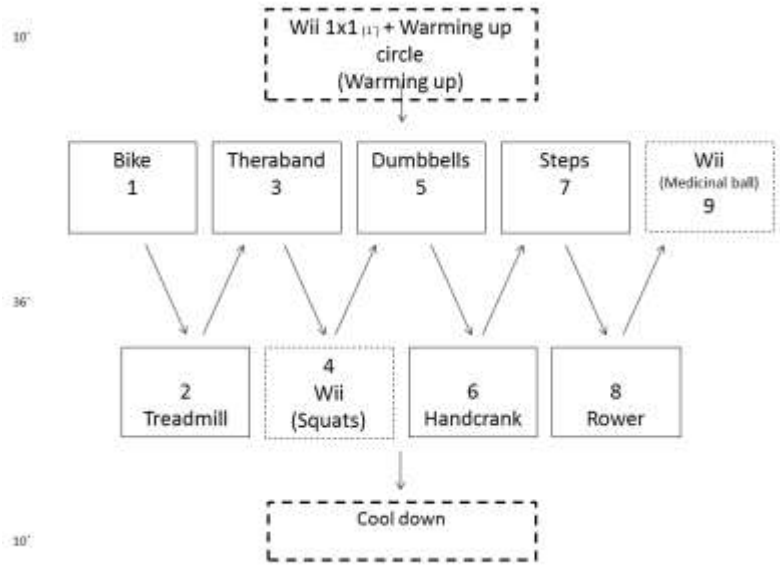

Fig1 – Exercise class circuit diagram; In parenthesis the control protocol

Both arms will be clustered in non-overlapping 1 hour supervised rehabilitation classes, either using Wii or not, catering for 6-10 patients, scheduled to 2 different non-consecutive week days (e.g. class 1 – Mondays and Wednesdays, class 2 – Tuesdays and Thursdays). Both groups will be subjected to equal exercise load (55-70% target heart rate for a maximum of 36 minutes,) for 6 weeks, under CR programme coordinator supervision. Intensity prescription will be based on pre-exercise stress test.. Only one motivational telephone call will be done, by the CR programme coordinator, for those at risk for not completing the programme, namely, after second class missing. Patients will be assessed at outpatient clinic at baseline, 6 weeks (end of exercise program) and 8 weeks of follow-up (14th study week), by experienced cardiologist blinded to subjects' allocation (Fig 2). Non-adherers will also be assessed at the same time points, since these evaluations are part of their normal Cardiology follow-up agenda.

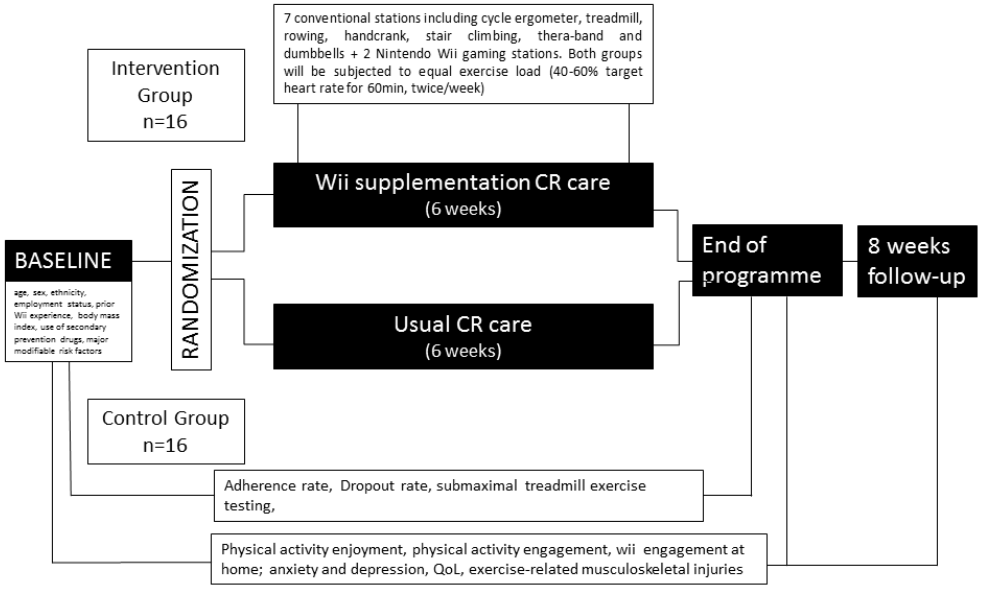

Fig2 –Study design

Volunteers will be supervised by the research team, and monitored by telemetry according to risk stratification, at all times throughout the exercise experimental protocol. The CR programme coordinator holds an advance life support certificate. The study will take place in the grounds of the partner Hospital so in the event of an adverse outcome, emergency services can be accessed promptly.

2.4 Outcomes

The intervention and control will produce the following read-outs:

Primary outcome:

- Attendance rate

Individual attendance rate, the main intention-to-treat outcome measure, will be defined by the number of attended sessions over the total number of sessions in the programme (percentage).

Secondary outcomes:

- Dropout rate
- Exercise capacity
- Physical activity engagement
- Physical activity enjoyment
- Anxiety and/or Depression
- Quality of Life
- Exercise-related musculoskeletal injuries
- Motor-coordination skills
- Audiovisual supplemented exercise engagement at home

Secondary outcome measures will be registered at the 6th week (end of programme) and at 8 weeks of follow-up (14th study week), with the help of the attending cardiologist: dropout rate will only be sought by the end of the programme, and defined by participants voluntarily missing more than 3 consecutive sessions or attendance <60% of sessions, otherwise with no medical contraindication; exercise capacity in METs will be assessed by submaximal treadmill exercise testing, supervised by technicians) also exclusively at the end of the programme; diagnosed exercise-related musculoskeletal injuries will be recorded; physical activity enjoyment and engagement, anxiety and depression and quality of life will be assessed as described previously for baseline.
These questionnaires are additional to usual care, but may be used by the physician when needed as diagnostic or prognostic tools, when certain conditions are likely associated: HAD scale for anxiety and depression, MacNew questionnaire to assess quality of life as an independent cardiovascular risk factor, or the PANNAS scale to assess enjoyment through exercise when the physician is suspicious that the patient may not be motivated towards it.
Motor-coordination baseline skills and technique progression (Wii related for the intervention arm) will be grossly evaluated by the CR programme coordinator at week 1 and by the end of the 6th week (well adapted, intermediate adaptation, maladapted); Audiovisual supplemented exercise engagement at home will be assessed by self-reported nº hours/week playtime.

2.5 Power and sample size

A pilot study may enable us to detect an increase in the adherence rate and reduction in the percentage of drop outs among the intervention arm, the latter rated at 32% nationally [7], when compared to the controls. A general rule of thumb is to take around 30 patients to estimate a given outcome [18], therefore we will respect this numbers (n=32).
Locally, the number of patients who went through the unit in 2010 is 64, derived from a CR uptake rate of 65% (referrals that enroll in the exercise programme in the first place). Therefore, we will require half of last year's CR population to achieve the desired sample size, allowing for a reasonable margin of non-participants.
According to the obtained effect size, one will be able to determine the power and sample size calculation for a future, larger prospective study, by using G*Power 3 software.

2.6 Randomization

After confirming subject eligibility and obtaining the informed written consent, the main researcher will randomize permuted blocks of eight patients (ratio 1:1), using a computerized algorithm (SPSS v.19 for PC), thus guaranteeing equal distribution of patients between the interventions (proportion 0,5).

Once the list of random order of assignment to study groups is generated, it will be applied to participants in strict sequence as they enter the trial. The CR programme coordinator will not have any contact with the random assignment procedure, a function of the main researcher, who will have no access to the actual setting nor the patients.
Random treatment assignments will be placed in advance in a set of sealed envelopes by the main researcher. Each envelope will be numbered, opaque, sealed and otherwise tamperproof. When a participant is randomized, his name is first recorded in the numbered envelope in the presence of a second staff member and both sign the envelope; then the envelope is opened and the randomization number contained therein assigned to the participant.
We believe that using either a match pairing strategy or stratified block randomization for possible confounders, such as age, sex, school degree, employment status and prior exergaming experience matched intervention, will be too restrictive, and not render good generalizability to the CR population, therefore impairing the translation of the results into practice.

2.7 Blinding and confidentiality

Both the assistant cardiologist, responsible for the outcome assessment, and the main researcher, who will analyze all data, will be blinded to the allocation of the participants (Fig3). Although, not blinded to treatment allocation, participants will be instructed by the CR coordinator not to reveal any information about their treatment, nor will they be told about the different exercise regimes available. Since classes are on different days it is unlikely they talk to different group members. The class providers will be instructed with detail how to avoid biased instructions to participants. an

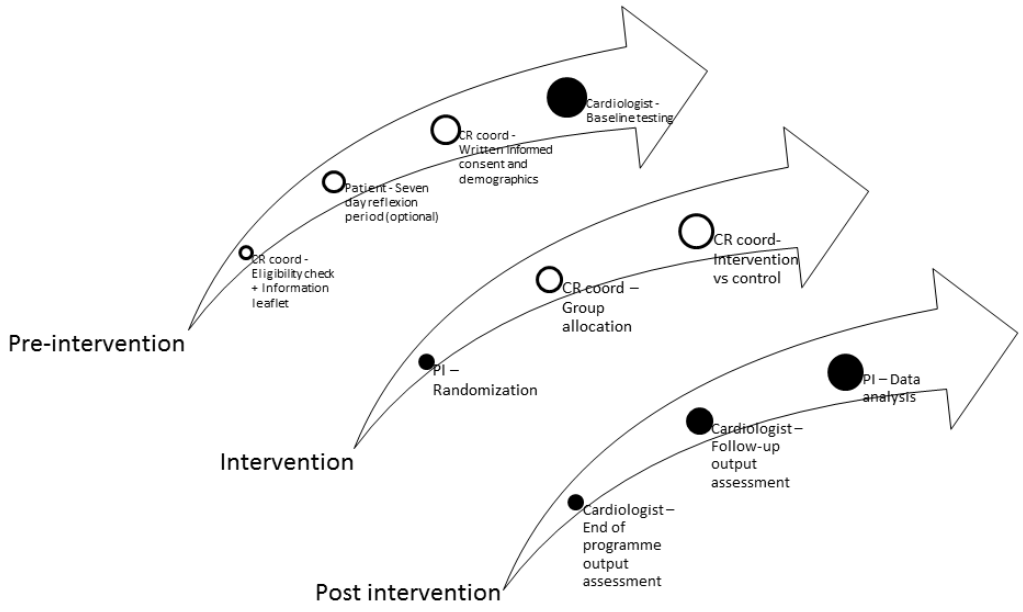

Fig 3 – Study intervention stages; filled circles correspond to blinded investigators

Again, data will be anonymous to the main researcher who will be conducting the statistical analysis. the CR programme coordinator, and never disclosed to the main researcher.

After randomization, each participant will be assigned a sequential number which will be used instead of the name in all records. Data will be extracted by the CR rehabilitation coordinator and fellow cardiologist to a patient datasheet, through direct inquiry, clinical process consultation, questionnaire answers and exam testing (stress test and accelerometry), all under clinician-patient privilege, therefore confidential. The sheet will be stored in safe location, and only handed to the main researcher by the end of the study follow-up. The linking codes will be in the possession of the CR programme coordinator, and never disclosed to the main researcher until statistical analysis have been completed.

2.8 Statistical methods

Demographic and baseline characteristics of patients will be collected by the CR class supervisor and descriptive statistics calculated by the main researcher.
For the primary outcome, logistic regression will be used to test the interaction of between drop out (yes/no) from the program and exercise strategy. To examine intervention and control groups secondary outcome significant differences, mainly in the clinical variables, t tests and χ^2 tests will be used for comparison of continuous and categorical variables, respectively. Odds-ratio with 95% confidence intervals will be calculated for categorical outcomes such as hospital admission (yes/no) to test association and risk factors. A probability value of <0.05 will be considered statistically significant. Data management and statistical analyses will be conducted using SPSS for windows v19.0.

2.9 Timetable

November 2012	Starting Date; Literature review and methodology writing; Visit pilot CRP center assess local conditions for trial implementation. Brief to Nurses and Physiotherapists
January to July 2012	Patient recruitment and assessment of eligibility. Random allocation of the included patients to 2 groups (case and control); Patient Follow-up and data collection
August to September 2012	Writing up

Table 1 – Project timetable. *Duration: 12 months; Collection of baseline data on a rolling basis

2.10 Planned Dissemination

- Paper publication
- Presentation of Results at Europrevent 2014 congress

2.11 Registration

The trial will be registered after Ethics Committee approval.

2.12 Funding

The study does not have any source of funding and other support to disclaim.

3. References

1. Ryden, L., J. Martin, and S. Volqvartz, *The European Heart Health Charter: towards a healthier Europe.* Eur J Cardiovasc Prev Rehabil, 2007. **14**(3): p. 355-6.
2. Graham, I., et al., *European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts).* Eur J Cardiovasc Prev Rehabil, 2007. **14 Suppl 2**: p. S1-113.
3. Giannuzzi, P., et al., *Secondary prevention through cardiac rehabilitation: position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology.* Eur Heart J, 2003. **24**(13): p. 1273-8.
4. Dalal, H.M., et al., *Home based versus centre based cardiac rehabilitation: Cochrane systematic review and meta-analysis.* BMJ, 2010. **340**: p. b5631.
5. Suaya, J.A., et al., *Cardiac rehabilitation and survival in older coronary patients.* Journal of the American College of Cardiology, 2009. **54**(1): p. 25-33.
6. Kotseva, K., et al., *EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries.* Eur J Cardiovasc Prev Rehabil, 2009. **16**(2): p. 121-37.
7. Cooney, M.T., et al., *EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) III--a comparison of Irish and European results.* Ir Med J, 2009. **102**(4): p. 113-6.
8. Marzolini, S., et al., *Self-reported compliance to home-based resistance training in cardiac patients.* Eur J Cardiovasc Prev Rehabil, 2010. **17**(1): p. 35-41, quiz 42-9.
9. Kerins, M., G. McKee, and K. Bennett, *Contributing factors to patient non-attendance at and non-completion of Phase III cardiac rehabilitation.* Eur J Cardiovasc Nurs, 2011. **10**(1): p. 31-6.
10. Davies, P., et al., *Promoting patient uptake and adherence in cardiac rehabilitation.* Cochrane Database Syst Rev, 2010(7): p. CD007131.
11. Beswick, A.D., et al., *Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.* Health Technol Assess, 2004. **8**(41): p. iii-iv, ix-x, 1-152.
12. Ridley, K. and T.S. Olds, *Assigning energy costs to activities in children: a review and synthesis.* Med Sci Sports Exerc, 2008. **40**(8): p. 1439-46.
13. Young, T.L. *U got 2 move it pilot study: Impact of an after-school interactive video exertainment program for underserved children*. in *Dissertation abstracts international: Section B: The Sciences and Engineering*. 2008.
14. Willems, M.B., T, *Comparison of Physiological and Metabolic Responses to Playing Nintendo Wii Sports and Brisk Treadmill Walking.* Journal of Human Kinetics, 2009. **2**: p. 43-50.
15. Ramchandani, A., Carroll, K, Buenaventura, R, Douglas, J, Liu, J. *Wii-habilitation increases participation in therapy*. in *Virtual Rehabilitation*. 2008. IWVR.
16. ACSM, *ACSM's Guidelines for Exercise Testing and Prescription*, 2009, Lippincont, Williams & Wilkins.
17. Piepoli, M.F., et al., *Secondary prevention through cardiac rehabilitation: physical activity counselling and exercise training.* European Heart Journal, 2010. **31**(16): p. 1967-1974.
18. Browne, R.H., *On the use of a pilot sample for sample size determination.* Stat Med, 1995. **14**(17): p. 1933-40.