CRIB— the use of cardiac rehabilitation services to aid the recovery of patients with bowel cancer: a pilot randomised controlled trial (RCT) with embedded feasibility study

Julie Munro,1 Richard Adams,2 Anna Campbell,3 Sandra Campbell,4 Cam Donaldson,5 Jon Godwin,5 Sally Haw,1 Lisa Kidd,5 Chrissie Lane,6 Stephen J Leslie,8 Helen Mason,5 Nanette Mutrie,7 Ronan O’Carroll,8 Cara Taylor,9 Shaun Treweek,10 Angus Watson,6 Gill Hubbard1

ABSTRACT

Introduction: Patients with colorectal cancer report ongoing physical and psychological impairments and a high proportion of these patients are overweight, insufficiently active and high-risk drinkers, putting them at risk of poor recovery and risk of recurrence and comorbidities. A challenge is implementing sustainable and effective rehabilitation as part of routine care for this group.

Methods and analysis: A two-arm pilot randomised controlled trial (RCT) with embedded feasibility study undertaken as a phased programme of work. The intervention involves an existing cardiac rehabilitation programme for cardiac patients accepting colorectal cancer patient referrals. The intervention consists of supervised exercise sessions run by a cardiac physiotherapist and information sessions. Phase 1 will involve one research site enrolling 12 patients to assess intervention and study design processes. Semistructured interviews with patients with colorectal cancer and cardiac patients and clinicians will be used to gather data on acceptability of the intervention and study procedures. Phase 2 will involve three sites enrolling 66 patients with colorectal cancer randomised to control or intervention groups. Outcome measures will be taken preintervention and postintervention, for phases 1 and 2. The primary outcome is accelerometer measured physical activity; secondary outcomes are self-report physical activity, quality of life, anxiety, depression, symptoms including fatigue. The following variables will also be examined to determine if these factors influence adherence and outcomes: self-efficacy, risk perception and treatments.

Ethics and dissemination: Full ethical approval was granted by NRES Committees—North of Scotland (13/NS/0004; IRAS project ID: 121757) on 22 February 2013. The proposed work is novel in that it aims to test the feasibility and acceptability of using an evidence-based and theory driven existing cardiac rehabilitation service with patients with colorectal cancer. Should this model of rehabilitation prove to be clinically and cost effective we aim to conduct a randomised controlled trial of this intervention to measure effectiveness.

Strengths and limitations of this study

▪ This is the first study to test the feasibility and acceptability of cardiac rehabilitation for patients with colorectal cancer.
▪ The study will also test if it is feasible and acceptable to deliver rehabilitation to mixed clinical population groups (ie, myocardial infarction and colorectal cancer).
▪ This is a pilot randomised controlled trial with an embedded feasibility study and therefore will not report on the effectiveness of cardiac rehabilitation for patients with colorectal cancer.

INTRODUCTION

Over two million people are living with cancer in the UK, and this number is rising by 3% per annum1 and includes approximately 150 000 people diagnosed with colorectal cancer.2 Increasing incidence and survival, and a growing awareness of the physical and psychological long-term and late-term effects of cancer and its treatments,3 means that there is growing demand for rehabilitation. Recent evidence presents a strong case for the provision of rehabilitation services for patients with colorectal cancer. Around 30% of patients with colorectal cancer report on-going physical and psychological impairments.3 ▪ A high proportion...
are overweight, insufficiently active and high-risk drinkers, putting them at risk of poor recovery and risk of recurrence and comorbidities. Yet, colorectal cancer survivors report among the lowest physical activity participation rates of any cancer survivor group and have been shown to perform considerably less physical activity after their diagnosis than they did before. This suggests potential room for improvement in levels of physical activity if given appropriate support.

Observational studies have highlighted the benefit of exercise (a core component of cardiac rehabilitation) for colorectal cancer survivors. In a study involving 832 people with stage iii colon cancer indicated that higher levels of self-reported physical activity approximately 6 months after completion of chemotherapy were associated with superior disease-free, recurrence-free and overall survival. A study of 668 men diagnosed with stages i–iii colorectal cancer also found that increased physical activity was significantly associated with improved colorectal cancer-specific mortality and overall mortality. These observational studies suggest that interventions to increase physical activity in colorectal cancer survivors may help to improve disease outcomes. Moreover, it has been suggested that the magnitude of the associations between physical activity and disease outcomes reported in these observational studies compares favourably with the benefit observed with the use of adjuvant chemotherapy, but would likely involve lower toxicity and cost.

Five recent systematic reviews of controlled trials indicate that physical activity interventions can help address the physiological and psychosocial effects of cancer and associated treatments in adult patients with cancer. While together these reviews demonstrate the benefits of exercise interventions, a note of caution is required because the results of these studies cannot be automatically generalised to patients with colorectal cancer. This is because patients with colorectal cancer relative to patients with breast cancer (the most featured group of patients in reviewed studies) present with more advanced disease, have different treatments and symptoms, tend to be older and include equal numbers of men and women.

Cardiac rehabilitation may be an appropriate form of rehabilitation for patients with colorectal cancer because many of their needs post-treatment are similar to those individuals living with coronary heart disease. Studies on patients’ experiences of needs after coronary artery bypass grafting and patients with colorectal cancer indicate that patients with cardiac issues and cancer experience similar problems including pain, fatigue, anxiety and depression, worry, appetite loss, sexual problems, sleep disturbance, and work and financial-related difficulties and express a need for information about medication and self-management. Thus, the rehabilitation needs of patients with coronary heart disease and patients with colorectal cancer are likely to be similar. Pointing out the similarities in post-treatment experiences is not to deny that disease-related differences exist. Patients with colorectal cancer may specifically experience physical discomfort and bowel function problems and urinary tract infections and need advice about abdominal pain and stoma care. The comparative evidence, however, suggests that a common rehabilitation programme may be appropriate for meeting many of the needs of both groups. Moreover, cardiac rehabilitation may be particularly relevant for patients with colorectal cancer since the estimated prevalence of cardiovascular disease is 59% at 5 months postdiagnosis and 16% develop de novo cardiovascular disease within 36 months after treatment. This is why a study exploring the feasibility and acceptability of delivering cardiac rehabilitation to mixed classes of patients with cardiac issues and colorectal cancer with some disease-specific components delivered by experts in cardiac and cancer care, respectively, seems worthwhile.

**AIMS AND OBJECTIVES**

The purpose of the study is to conduct a pilot randomised controlled trial (RCT) of an existing cardiac rehabilitation service versus usual care (no routine National Health Service (NHS) rehabilitation provision) to aid the recovery of patients with colorectal cancer. The pilot RCT with embedded feasibility study will be conducted to inform the design and conduct of a future larger scale effectiveness trial for which separate funding would be required.

The overall aims of this essential preliminary work are to:

1. Assess the potential of an existing cardiac rehabilitation service taking colorectal cancer patient referrals to improve health outcomes for patients with cancer.
2. Refine the intervention and trial procedures for a future full-scale effectiveness RCT.

**Phase 1: feasibility study objectives**

1. To assess the feasibility of delivering rehabilitation to patients with cancer within a cardiac rehabilitation setting.
2. To assess the acceptability of the intervention for patients and clinicians (cancer and cardiac).
3. To assess the acceptability and adequacy of the training and support provided by a cancer-exercise specialist for cardiac physiotherapists running the rehabilitation exercise classes.
4. To assess the feasibility and acceptability of the main trial components (eg, recruitment procedures, rehabilitation referral procedures and proposed outcomes and process measurement tools) and proposed tools for measuring impacts on outcomes and costs.

**Phase 2: pilot study objectives**

5. To determine eligibility, consent, recruitment and retention rates and speed of recruitment.
6. To determine likely contamination across trial arms.
7. To determine completion rates for proposed outcomes measurement tools at baseline and follow-up.
8. To provide data for sample size calculation for a definitive RCT.
9. To test intervention fidelity according to study protocol.
10. To assess the extent to which intervention and trial procedures can be integrated into routine clinical practice.
11. To conduct a preliminary economic evaluation of the cancer rehabilitation programme.

METHODS AND ANALYSIS

Design
This is a two-arm pilot RCT with an embedded feasibility study that will be undertaken as a phased programme of work comprising intervention testing and feasibility work (phase 1) and a pilot trial with a process evaluation (phase 2). An economic evaluation will be carried out to establish the cost component of this particular intervention. In line with Medical Research Council guidance on the development and evaluation of complex interventions, a preliminary phase is included, which focuses on intervention refinement and feasibility and a qualitative process evaluation of the pilot RCT in order to ensure that both the intervention and trial procedures are optimised and can be incorporated into routine clinical practice, thus increasing the likelihood that a full-scale trial will generate the desired outcomes. The study will be conducted according to recommendations for good practice in pilot studies.

Setting
The study will be conducted in three cardiac rehabilitation facilities in three NHS Boards across the UK: NHS Highland, Highland Heartbeat Centre, Raigmore Hospital; NHS Wales, University Hospital of Wales and Maindy Sports Centre, Cardiff; NHS Forth Valley, NHS Hub at the Peak sports and leisure complex, Stirling.

Participants

Inclusion
1. Adults who have been diagnosed with primary colorectal cancer and are in the recovery period postsurgery.
2. Patients may be receiving adjunctive chemotherapy/radiotherapy. Patients must wait 48 h postchemotherapy before taking part in the intervention.

Exclusion
1. Patients with advanced disease.
2. Patients who fail clinical/risk assessment for rehabilitation and are deemed unsafe to participate in exercise classes. (According to recent guidelines, those with severe anaemia should delay exercise and patients with compromised immune function should avoid public gyms and exercise classes.)

3. Patients with severe cognitive impairment and therefore are unable to give informed consent to participate in the study, or are unable to communicate in English since this is the language used in cardiac rehabilitation.

Cardiac patients who have attended cardiac rehabilitation classes with patients with bowel cancer, and colorectal cancer and cardiac clinicians involved in the study will also be included.

Sample size
For the feasibility study (phase 1) 12 patients with colorectal cancer will be recruited to assess the feasibility and acceptability of the intervention, recruitment processes for the trial and study instruments. In addition, six cardiac patients and six clinicians will also be recruited to assess the feasibility and acceptability of the intervention and recruitment processes.

For the pilot RCT (phase 2), a power calculation is not appropriate as the study does not aim to provide a definitive estimate of treatment effect. Rather the aim is to provide robust estimates of the likely rates of recruitment and retention, and to yield estimates of the variability of the primary and secondary outcomes to inform power calculations for a future large-scale trial. The pilot trial (phase 2) will be used in order to provide a quantitative estimate of the intervention impact (relative to control) in order to inform the sample size estimation for a future definitive trial. For the pilot RCT (phase 2), over 6 months, we expect 250 patients to be approached over the three sites. Responses will determine whether it is possible to recruit patients and also estimate eligibility, consent, participation and retention rates and speed of recruitment for a future large-scale trial. Cancer clinicians estimate that approximately one-third will be ineligible (eg, have advanced disease) and based on recruitment to an RCT about physical activity with patients with cancer in Scotland (27% recruitment rate) and a trial involving patients with colorectal cancer within 3 months of completing surgery conducted in Canada (35% recruitment rate), we estimate that about a third of eligible patients will consent. Thus, for the pilot RCT we expect to recruit 66 patients.

Intervention
The intervention is cardiac rehabilitation delivered to patients with colorectal cancer within a traditional cardiac rehabilitation programme setting. This consists of an 8/12 week programme (depending on research site) to a mixed patient with cardiac issues/ cancer class with some information (eg, about treatment-related symptoms) specifically tailored to the different patient groups. Classes will be delivered once or twice a week, and consist of 60–90 min of aerobic and strength training and educational sessions, delivered by a range of health professionals (the specific components of the exercise and educational sessions may be variable depending on research site). Educational sessions will either be...
delivered to a group of patients with cancer separately from the cardiac patients (eg, sessions discussing specific drug treatments) or one-to-one by telephone (depending on research site). Participants will set individual physical activity goals with advice and support from the physiotherapist. Cardiac physiotherapists will pragmatically apply underpinning health behaviour theories by, for instance, discussing barriers to engaging in physical activity with patients and goal setting, which is in line with current behaviour change theory30–33 and cardiac rehabilitation guidance,34 to encourage translation of knowledge into behaviour change. To optimise intervention fidelity, professionals delivering the intervention will be expected to follow their site-specific rehabilitation programme. Patients randomised to the control arm of the pilot RCT (phase 2 of the study) will receive ‘Staying healthy after bowel cancer’ booklet by Bowel Cancer UK, which includes a section on ‘staying fit’.35

Outcomes
Primary outcome
Physical activity will be assessed using the Actigraph GT1M accelerometer (Actigraph LLC, Pensacola, Florida, USA).36–38 Participants will be asked to wear an accelerometer for 7 days on three occasions (T0—before patients are randomised to the intervention or control group; T1—at the end of the intervention (data will be collected 12 weeks after baseline for patients in the control arm); and T2—3 months later). Physical activity will also be assessed subjectively using the Scottish Physical Activity Questionnaire.39

Secondary outcomes
The proposed secondary outcomes in a future large-scale trial will be the difference in measures of quality of life, anxiety and depression and fatigue between the intervention and usual care (control) group. Data on these will be collected in the proposed feasibility study and pilot trial.

Quality of life: EQ-5D, which is a parsimonious measure of health-related quality of life consisting of five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, will be used to measure quality of life.40 A recent review shows a substantial and growing body of literature using the EQ-5D in cancer, and draws the conclusion that it is a valid and reliable instrument.41 The Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument, which combines specific concerns related to colorectal cancer with concerns that are common to all patients with cancer will also be used.42

Anxiety and depression: The Hospital Anxiety and Depression Scale (HADS), which consists of 14 questions, 7 for anxiety and 7 for depression, will be used to measure anxiety and depression.43 A meta-analysis suggests that it is sufficiently sensitive for identifying depression and anxiety in patients with cancer.44

Fatigue: The Functional Assessment of Cancer Therapy Fatigue (FACT-F),45 which is a 13-item fatigue FACT subscale, will be used to measure cancer-related fatigue.

Process variables
Physical activity self-efficacy and risk perception will be measured to assess if these psychological constructs predict attendance at cardiac rehabilitation classes and changes in health outcomes arising from the intervention. Physical exercise self-efficacy is the belief that one can engage in, and meet physical activity goals. According to the behaviour motivation hypothesis,46 perceived risk is positively and directly related to health behaviour. Risk perception of suffering from diseases has been found to play an important role in the development of intentions to perform physical activity among older adults47 and in explaining cancer-related behaviours.48

Clinical variables
In addition, the following clinical confounding factors will be assessed: colon or rectal surgery; surgical intervention (eg, laparoscopic or open surgery); temporary (a loop ileostomy) or permanent stoma or no stoma; chemotherapy or no chemotherapy (including duration and type of chemotherapy); any radiotherapy treatments.

Feasibility study (phase 1): recruitment, consent and data collection
Recruitment dates
Recruitment for phase 1 is between 1 July 2013 and 31 December 2013.

Phase 1: recruitment and consent
Patients with Cancer: The following recruitment methods will be employed in phase 1 for patients with colorectal cancer. First, a colorectal cancer clinical nurse specialist will screen all patients with colorectal cancer admitted for surgery to assess their eligibility for the study. The nurse will give eligible patients an information sheet about the study and talk them through it. If the patient agrees to participate the nurse will ask them to sign a consent form and then refer the patient to the researcher who will then inform cardiac rehabilitation about the patient by email, fax or letter. Patients who decline to participate having read the study information will be asked if they would be willing to complete a questionnaire about reasons for declining to participate. Second, a member of the cardiac multidisciplinary team (eg, cardiac physiotherapist or nurse) will contact patients with cancer and invite them to attend a cardiac rehabilitation clinical/risk stratification assessment to determine whether the patient will be able to safely exercise from a cardiac clinical perspective and plan physical activity goals tailored to individual patient needs. Patients who are deemed safe to exercise will be invited to attend cardiac rehabilitation classes. Patients who decline to attend a clinical/risk stratification assessment
will be asked if they would be willing to complete a questionnaire about reasons for declining to participate.

**Cardiac patients**: All cardiac patients will be informed that the study is taking place at the cardiac rehabilitation facility and that the classes that they attend may include patients with cancer. At the end of the intervention, six cardiac patients who attended rehabilitation classes at the same time as patients with cancer will be approached by a researcher and invited to attend a semistructured face-to-face interview about their experiences of having patients with cancer participate in rehabilitation. Patients will be purposively sampled so that the study includes responses from younger and older men and women.

**Clinicians**: Cancer and cardiac clinicians involved in screening and recruitment and/or delivering the intervention will be approached by a researcher and invited to attend a semistructured face-to-face interview about their experiences of the trial procedures and the intervention.

**Phase 1: Data collection**

A screening and recruitment log will be completed by a researcher to document all patients considered for the study and subsequently included or excluded at each stage of the recruitment process and reasons given. This will include information such as when the patient was given information about the study, referred to cardiac rehabilitation, attended for clinical/risk assessment and received an offer to attend rehabilitation classes. During the cancer patient’s attendance of the cardiac rehabilitation programme, a researcher will contact the patient each week to complete an intervention record log that will document the number of classes attended by participants, type and duration of exercises and which education classes the patient attended. On completion of rehabilitation, semistructured face-to-face interviews will be conducted with, (1) 12 patients with cancer and a nominated family member, (2) 6 cardiac clinicians who were involved in screening, recruitment, referral and/or delivering the intervention and (3) 6 cardiac patients involved in the mixed cancer/cardiac patient rehabilitation classes, in order to gather responses about the acceptability of the intervention and trial procedures. Twelve clinicians involved in recruitment and/or delivering the intervention split between the research sites will also be interviewed. Outcome measures will be collected at baseline, on completion of the intervention, and at 3 month follow-up.

**Phase 2: Randomisation**

Patients will be randomised to the intervention or control group after they have consented to participating in the study and after baseline primary and secondary measures have been collected. Randomisation with stratification by centre will be conducted by Tayside Clinical Trials Unit.

**Phase 2: Data collection**

As in phase 1, a screening and recruitment log will be completed by a researcher to document all patients considered for the study and subsequently included or excluded at each stage of the recruitment process and reasons given and a researcher will contact the patient each week to complete an intervention record log. On completion of rehabilitation, semistructured face-to-face interviews will be conducted with 24 patients with cancer with equal split between research sites to gather responses about the acceptability of the intervention and trial procedures. Twelve clinicians involved in recruitment and/or delivering the intervention split between the research sites will also be interviewed. Outcome measures will be collected at baseline, on completion of the intervention, and at 3 month follow-up.

**Analysis**

All qualitative data will be analysed in order to address objectives 1–4 and 10. Audiorecorded interviews will be transcribed verbatim. Transcripts will be analysed thematically using the framework approach, which is a rigorous method that provides a structure within which qualitative data are organised and themes within and between groups of participants (eg, between patients and clinicians) are identified. Inter-rater reliability will be performed between the researchers conducting analysis. Quantitative data will generate the following: estimates of eligibility, consent, recruitment and retention rates and speed of recruitment (objective 5); estimates of completion rates of study assessment tools (objective 7); estimates of contamination between intervention and control groups (objective 6); estimates of intervention fidelity (objective 9). Descriptive presentations of the proposed primary and secondary outcomes will also be made to inform a sample size calculation for a large-scale trial and decisions as to whether their inclusion would be informative in a future trial (objective 8). Finally, comparisons between intervention sites on recruitment, retention and likely health outcomes, etc will be made to inform development of intervention and main trial components for a future large-scale trial.

**Economic evaluation**

Following previous research on the economics of cardiac rehabilitation, the economic evaluation will involve three main components: assessment of costs of the
rehabilitation programme itself; estimation of further impacts on healthcare use; and bringing these two elements of cost together with data on outcomes described above. NHS programme costs will be estimated on a per patient basis as the sum of costs of space rental, equipment (amortised over usual estimates of life cycles for such items), staff costs (using NHS wage rates in programme sites) and other programme consumable items (such as rehabilitation literature, again to be estimated from cost data at local programme sites). At local programme sites, financial records will be examined as well as interviews with finance and care staff, in order to assess actual impacts of providing the programme on the costs listed above—space and equipment provision, staff costs and any consumable items used. These data will also provide a basis for making further assumptions about cost impacts in other geographical locations. Information to be obtained on patient-borne costs will be obtained by embedding questions in the data collection instrument. This will cover: distances travelled; transportation types; shoes, clothing and other equipment purchased to participate; child care expenses; and total time attending the programme. Where relevant, patients will be asked to estimate actual monetary costs incurred by them for using or purchasing these items, but otherwise will impute data on prices of such items where respondents cannot recollect monetary amounts.

In addition, at each assessment with intervention and usual care groups, information will be collected on: general practitioner visits; hospital emergency department visits and hospital admissions; visits to allied health departments such as physiotherapy and occupational therapy, nutrition, social work and vocational rehabilitation (from patient questionnaire). Patients will also be asked to report on any medications used. Data on hospital visits and drug use will also be available through NHS records. Data on rehabilitation programme costs and those on further impacts will be aggregated and the statistical significance of differences in cost per patient between intervention and control group assessed by appropriate methods depending on the distributional characteristics of the data.

ETHICS AND DISSEMINATION

Recent policy recommends that cancer rehabilitation is specified in Service Level Agreements in commissioning contracts and government cancer strategies recommend rehabilitation. Yet, rehabilitation is not strongly articulated in commissioning and local cancer care pathways often do not explicitly refer to rehabilitation. Research to examine how the NHS might improve delivery of rehabilitation services to effectively and efficiently aid the recovery of patients with cancer will help to address this gap. In developing this proposal, particular attention has been paid to addressing a current gap in service provision: the lack of a sustainable and cost-effective cancer rehabilitation NHS service capable of being integrated into the routine follow-up care of people affected by cancer. The proposed work is novel in that it aims to test an existing, evidence-based and theory driven cardiac rehabilitation service for patients with colorectal cancer. Should this model of rehabilitation prove to be clinically and cost effective in a future definitive RCT, then referral pathways could be adapted to ensure that the model is integrated into existing cancer service frameworks. The future study is likely to be of particular interest and use to service commissioners and NHS cancer managers. However, it is important that the feasibility and acceptability of the proposed intervention and trial procedures are established first before moving to a full definitive trial; hence, this pilot RCT with embedded feasibility study is currently being conducted.

Author affiliations

1 School of Nursing, Midwifery and Health, University of Stirling, Stirling, UK
2 Cardiff University, School of Medicine, Velindre Hospital, Cardiff, UK
3 Institute of Sport and Exercise, University of Dundee, UK
4 NHS Forth Valley, Larbert, UK
5 School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK
6 NHS Highland, Inverness, UK
7 Moray House School of Education, The University of Edinburgh, Edinburgh, UK
8 School of Natural Sciences, University of Stirling, Stirling, UK
9 NHS Tayside, Level 10, Ninewells Hospital, Dundee, UK
10 Health Services Research Unit, University of Aberdeen, Foresterhill, Aberdeen, UK

Contributors GH and JM wrote the first draft of this article; all authors contributed to the final version of the article, designed the study, and are responsible for conducting the study.

Funding This work is supported by the National Institute for Health Research—Health Service and Development Research. Project reference number: NIHR—HS&DR Project:12/5001/09.

Disclaimer The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HS&DR Programme, NIHR, NHS or the Department of Health.

Competing interests None.

Patient consent Obtained.

Ethics approval Full ethical approval was granted by NRES Committees—North of Scotland (13/NS/0004; IRAS project ID: 121757) on 22 February 2013

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data sharing statement All anonymised data will be available on request to the study sponsor, which is the University of Stirling and the PI (GH).

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/3.0/

REFERENCES


34. BACPR. The BACPR Standards and Core Components for Cardiovascular Scand 1983;67:361–70.


CRIB—the use of cardiac rehabilitation services to aid the recovery of patients with bowel cancer: a pilot randomised controlled trial (RCT) with embedded feasibility study

Julie Munro, Richard Adams, Anna Campbell, et al.

*BMJ Open* 2014 4:
doi: 10.1136/bmjopen-2013-004684

Updated information and services can be found at:
http://bmjopen.bmj.com/content/4/2/e004684.full.html

**References**

This article cites 41 articles, 6 of which can be accessed free at:
http://bmjopen.bmj.com/content/4/2/e004684.full.html#ref-list-1

**Open Access**

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/3.0/

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**

Articles on similar topics can be found in the following collections

- Cardiovascular medicine (245 articles)
- Oncology (129 articles)
- Rehabilitation medicine (65 articles)
- Sports and exercise medicine (67 articles)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/