NCCHTA

13 February 2009

HTA no: 03/45/07
ISRCTN no: 16900744
UKCRN study ID: 2159
MREC no: 05/MRE07/42

Funded by the NHS R & D Health Technology Assessment Programme

A pragmatic randomised controlled trial to evaluate physical activity as a treatment for depression

TREAD

1. PLANNED INVESTIGATION

1a) *Research objectives*

The primary research question is "Does physical activity, in addition to usual care in primary health care, change the outcome in depression and alter the subsequent use of antidepressant medication?"

1b) *Existing research*

Depression is one of the leading reasons for disability in the UK, as elsewhere, and is the third most common reason for consulting a general practitioner. There are now over 25m prescriptions of antidepressants each year in primary care in England that cost £80m (www.ppa.org.uk). Antidepressants are an effective treatment for the more severe depressions but there is uncertainty and concern about the use of antidepressants, especially in those with mild depression. Adherence to antidepressant treatment is often poor and only about 20% of patients will take medication according to guidelines[1;2]. There is widespread scepticism about the effectiveness of antidepressants amongst the general population and this may contribute to a reluctance to consult general practitioners for depression[3]. Hence, there is a need to identify effective non-pharmacological interventions for the management of the common, less severe forms of depression and as a potential means of reducing the length of treatment with pharmacological agents.

Health benefits of physical activity
There has recently been an increased interest in the potential health benefits of physical activity in heart disease, obesity and diabetes[4]. In the past decade 'exercise on prescription' schemes have become popular in primary care in the UK. However, there has also been a suggestion that exercise (or it's more widely-defined counterpart, physical activity) could be an effective treatment of depression. Many of the 800 or so schemes in the UK receive referrals for people with depression (Wright Foundation Survey 2003).

A systematic review of randomised controlled trials (RCTs) by one of the Co-applicants[5] found evidence to support the effectiveness of exercise for depression, but it also identified some important methodological limitations which mean it is still uncertain whether physical activity is effective in the management of patients with depression in primary care. These issues can be summarised as follows:

(a) *lack of evidence in clinical populations*
The majority of RCTs have been conducted in non-clinical community volunteers who have responded to advertisements concerning an exercise in depression trial. In some studies, there were financial or other incentives to participate. Results from such trials are difficult to generalise to patients who present to primary care as volunteers are likely to have an extra degree of motivation.

(b) *short duration of follow-up*
Only one of the trials studied whether any benefits of an exercise intervention outlasted the duration of the intervention. In the meta-regression[5], the length of follow-up was an important source of heterogeneity, with those of shortest duration reporting the largest effects suggesting that effects may be weak or non-existent over the long-term. In the context of a chronic relapsing and remitting disease, it is important to estimate the long-term as well as the short-term effects, though even a short term benefit may still be cost-effective.

(c) *poor quality of trials*
The majority of trials to date used randomisation procedures that were inadequately concealed, failed to undertake intention-to-treat analyses or followed protocols involving unblinded treatment allocation. In general, these failures will tend to exaggerate treatment effects.[6]

(d) *small size of trials*
The trials undertaken to date were all far too small and underpowered to find anything apart from a massive treatment effect. The largest of the trials included just 36 participants in the treatment arm and 28 in the control arm; most trials had fewer than 20 participants in total.

In a recent update of the Lawlor systematic review, a number of new studies were reported.

The DOSE study[57] found a treatment response for the more intensive 'dose' of exercise in their trial. This intervention involved the participants attending a gym and carrying out aerobic activity on an exercise bike. The more vigorous (17.5 Kcal/kg/wk) and more frequent (five days) form of intervention appeared to have a benefit when compared to the control group. However, the study was small, with only sixteen subjects randomised to the most intensive group – overall there were eighty participants allocated to five groups with a Latin square design. Additionally, participants had very mild depression, with a mean Hamilton[31] score of 16.2, although all met DSM-IV[58]) criteria. The fact that this was a non-pragmatic trial in a different health care setting to TREAD means that vital issues about treating depression with physical activity remain unexplored.

Blumenthal et al[59] have also carried out a comparison, in the US, between two different exercise interventions, with antidepressant and placebo treatments. They found a 9% difference between remission rates as a result of home-supervised exercise and placebo at sixteen weeks. This difference is slightly smaller than that which we have used for the TREAD power calculations. However, we would expect a placebo effect in such trials, so we think that the plausible treatment difference between intervention and usual care would be greater than that reported in this particular trial. In addition, this was a relatively small trial with just over 40 participants in each group and so probably estimated these differences with little accuracy.

Another US trial, coincidentally called TREAD, is underway and has published its protocol[60]. The intervention in this case is modelled upon the more intensive intervention from the DOSE study, although it is somewhat more pragmatic since it allows home-based as well as gym-based activity. However, participants are sedentary at baseline and there were reported difficulties in implanting the intervention. The protocol paper does not state the overall sample size nor does it undertake any form of economic analysis.

Whilst the above-mentioned studies address some of the previously mentioned methodological concerns, there is no suggestion that they substantially change our original conclusions. None of them address the same aims as TREAD, nor do they deal with issues in a way which relates to the NHS. Thus, the scientific questions of our study are still relevant and of importance, particularly if we want to contribute to UK policy and practice.

How might exercise work?
Little is known about the possible mechanisms that might mediate any therapeutic effects of physical activity on depression. Suggested biological mechanisms include changes in neuro-endocrine function, neurotransmission, core temperature, cerebral blood flow, or muscular tension. Psychosocial mechanisms such as improvements in physical self-perceptions and self-confidence have been observed[9] and increased social interaction and perceived support from an exercise specialist or exercise group have also been suggested.

Similarly, there is little evidence to indicate the type, intensity and duration of physical activity that might be most effective in reducing depression. The recent CMO report[4] concluded, on the basis of rather limited evidence, that aerobic exercise lasting between 20 and 60 minutes which involved large muscle groups, such as brisk walking, cycling and swimming, was likely to be most effective. The Dunn[8] trial was designed to compare 180 and 80 minutes of moderate activity per week over 5 and 3 days (for each dose) and a stretching group, over 12 weeks.

A physical activity intervention, if effective, is likely to improve depressive symptoms through some or all of these pathways and it could be that the overall effectiveness of physical activity relies upon such multiple mechanisms. We, therefore, think that the priority, at this stage, is to determine whether physical activity might improve outcomes in patients with depression. The exploratory analyses and the qualitative elements of the proposed research will be of value in planning future, more detailed investigations.

How can we best encourage an increase in physical activity?
In order to investigate our research question, we need to design an intervention that will lead to a sustainable change in physical activity patterns. There are some systematic reviews [10,11,12,13,14] of RCTs that have investigated the ability of exercise promotion interventions to increase activity levels. In planning an intervention for depressed participants, there are four issues to consider:

1) intensity of the intervention
The reviews concluded that there is little evidence to suggest that the investigated interventions led to a long-term change in physical activity. However, this may have been because the interventions were not intensive enough in terms of the amount of supervision and support provided to participants. Very few of the interventions would meet the more recent NHS National Quality Assurance Framework (NQAF) guidelines for exercise referral schemes[15 16]. Many of the studies only had one contact with the patient and it is probably difficult to generalise from some of the US studies. In a UK study, Harland[17] concluded that progressively more intensive interventions, involving up to 6 counselling sessions and 30 free leisure centre vouchers produced greater changes in physical activity up to 12 weeks. However, the effects were not sustained at 12 months. Taylor's RCT in the UK[9;18], reported increased activity and fitness at 26 weeks in response to a 10-week exercise referral scheme in a local leisure centre and improved physical self-perceptions at 9 months.

Most of the literature concerns interventions designed for patients with cardiovascular disease, rather than depression. Depression is characterised by low motivation, fatigue and reduced self-esteem and these are likely to make it difficult to increase physical activity levels. All the RCTs that have investigated the effects of physical activity on depression have used supervised physical activity sessions rather than advice.[5] This most likely reflects the understanding by those undertaking such studies that a less intensive intervention is unlikely to alter behaviour in those with depression. An intervention that has been relatively successful in changing behaviour in a cardiovascular disease group may not, therefore, be intensive enough for a trial of people with depression. Physical activity is still regarded with some scepticism as an effective treatment for depression and, at this stage of knowledge, it would be important to ensure that any intervention gives the best chance for changing behaviour. We want to avoid what Tones[19] has called a "type 3" error, in which lifestyle interventions have (correctly) failed to show an effect on outcome because the intervention itself was too weak to change behaviour.

2) theoretical model underpinning intervention

Only half of the reported trials have described an intervention based upon a theoretical framework. The most popular frameworks used were designed to influence exercise cognitions and behaviour based on stage of readiness to become more active (Transtheoretical Model)[20;21]. A recent systematic review[14] concluded that "stage of readiness" based interventions have not, on the whole, been effective in increasing patient's physical activity in primary care but, as mentioned above, many of these interventions were probably not sufficiently intensive. Little[22] devised an intervention based upon the Theory of Planned Behaviour (TPB) and other behavioural techniques found that counselling sessions produced a trend towards greater change in physical activity, but only at one month follow-up and in patients without depression recruited through a postal request.

The wide range of components used within this intervention, as with others, makes it difficult to attribute any change in behaviour to the use of the TPB or any one particular theoretical model. Furthermore, TPB seems to be more useful in predicting more intense physical activity rather than the more modest levels likely to be seen in this population. In this situation, using the model of self-determination theory (SDT) would seem more appropriate, with self-determination being based on the perception of choice in engaging in any behaviour.[23] Self-determination theory proposes that real shifts in behaviour arise through heightened autonomy or personal ownership of behavioural success. Self-determination theory also suggests that steady incremental improvement in self-efficacy occurs through achievement of personally directed goals. It also maintains that autonomous change of this nature provides the basis of self-esteem improvement. Encouraging participants to take charge of their physical activity decisions and choices is, therefore, very important. This approach fits well with the principles of motivational interviewing[24] leading to better adherence and better motivation.[25] It also supports the view that choice of physical activity option, as described later, should improve adherence, especially over the longer term.[26]

It would seem both sensible and pragmatic to base an intervention for depressed subjects on an appropriate theoretical model[21;27] within the frameworks of self-determination theory[23] and social cognitive theory[54]. In practical terms, the key elements are likely to be an intervention that (a) assesses current attitudes to physical activity, perceived barriers and the readiness to change (b) utilises motivational interviewing techniques[24] to engage the patients own motivation rather than providing simple advice (c) offers choice of physical activity and rate of improvement and (d) that uses appropriate behavioural strategies that can increase self-efficacy[44] and self-determination.[25] We will check if participants' baseline expectancy of a treatment effect on depression predicts adherence to physical activity and an improvement in depression.

3) who delivers the intervention

Evidence from primary care suggests that existing health professionals are very inconsistent at providing advice about exercise and physical activity. For example, McKenna et al[28] found that GPs and practice nurses typically did little to promote physical activity and those who did were up to four times more likely to be active themselves. It appears that only health professionals with a commitment to physical activity tend to encourage an increase in activity in their patients. The intensity and nature of a physical activity intervention for depression suggests that individuals with both a commitment to the concept and a readiness to develop expertise are needed. If each practice were to devote a health professional to this task, the training would have to be less intensive and, since each professional would only be seeing a handful of patients, it would be difficult to develop any expertise in the area. For such reasons, many people, within and outside the Department of Health, have argued for a new type of health professional who has expertise in behavioural change, that we shall call a Physical Activity Facilitator (PAF) .

There is already a multiplicity of tasks for practice nurses and there are likely to be future shortages of health professionals as a result of the recent NHS plan. It, therefore, makes sense to expand the NHS workforce by recruiting Physical Activity Facilitators from those who are now emerging from undergraduate and postgraduate courses. If this model were to be adopted more

widely, it would also be easier to implement since it is much simpler to train one person who might cover ten practices, than to have to train a health professional from each of those practices. The establishment of the Register for Exercise Professionals (www.reps-uk.org/welcome.asp), alongside the NQAF launch in 2001, has helped to ensure that staff employed in exercise referral schemes have appropriate training, insurance and abide by a code of ethics comparable to professions allied to medicine.

4) reducing barriers to physical activity

Many people are reluctant to engage in physical activity, not only because of financial barriers, but also because of their own perceptions about physical activity and preference for different forms of physical activity. The more traditional 'exercise on prescription' schemes in UK primary care, have been termed *structured or centre-based activity* where the patient attends formal group sessions at a leisure or community centre. In contrast, *lifestyle or home-based activity* allows the individual to develop their own physical activity programme from home which primarily consists of brisk walking or cycling. Of course, many individuals combine both. In a recent Department of Health commissioned review, Fox et al[29] found no difference in adherence to these two programmes where patients were randomised. The critical issue is to maximise choice in order to increase chances of adherence. In some of the more progressive physical activity schemes, such as those being delivered in Somerset, participants are referred to a trained facilitator who will establish activity preferences, needs and fitness levels. The Somerset scheme has some 25 different physical activity options including individual programmes of walking and callisthenics in addition to leisure-centre based courses.

Summary

In summary, there is only limited direct evidence at this point to inform the design of interventions or services that might lead to long-term increases in physical activity in the UK primary care setting among depressed patients. There is no well worked out 'off the shelf' intervention. The Co-applicants intend to base the intervention on the principles outlined above. In particular, the intervention should (1) provide relatively intensive contact and support (2) be based upon established psychological models of behavioural change (3) be administered by a trained Physical Activity Facilitator (4) provide choice and (5) a financial subsidy, where needed, to reduce barriers. As part of the research, we will provide a standardised training and a manual both to ensure consistent delivery of the intervention in the study and to aid wider implementation if that were indicated. The intervention will be based upon the Somerset scheme and the NHS National Quality Assurance Framework for Exercise Referral Schemes[15].

2) RESEARCH METHODS

2a) Study design

We are proposing a two-arm, multi-centre, pragmatic, randomised controlled trial with randomisation at the level of the individual participant.

Definition of usual care

It is difficult to define 'usual care' of depression in primary care. Some people with depression are managed without antidepressant medication but we suspect that this group have a milder illness[30], would be prescribed antidepressants if their symptoms persisted and would be more difficult to recruit to a study, since GPs might not have discussed the diagnosis with their patients. Any pragmatic trial of physical activity would be non-blinded, so if participants were not receiving antidepressants at the outset this could lead to a difference in antidepressant prescription between groups. For example, if participants who are not currently treated with antidepressants are randomised to usual care, the general practitioner (GP) might be more likely to prescribe antidepressants in view of the need to provide the individual with something more tangible in the way of treatment.

We are also interested in the use of medication over a longer term follow-up such as that specified in the research brief. The use of medication will doubtless be very different between individuals who are on antidepressants at the beginning of the trial and those who are not. For these reasons, we propose that the randomisation should be stratified according to whether the patient is taking antidepressants prescribed by their GP at the entry of the trial. The proposed analysis will also take these matters into account. Counselling and, on occasions, other psychotherapies, is used in primary care as an element of 'usual care'. This will also affect the design and interpretation of the proposed trial. However, the delay that inevitably occurs before counselling or psychotherapy are received will make it unlikely that this would affect our primary outcome or have a major impact on the trial. For this reason, we will not use it as a minimisation factor in our analysis.

Contamination
In an individually randomised trial, there is a possibility that subjects not randomised to physical activity will inadvertently have a form of usual care in which physical activity is given far more prominence or that participants on usual care would pursue their own programme of physical activity. This 'contamination' of the usual care group could reduce any observed treatment effect. Subjects randomised to usual care will not have access to the Physical Activity Facilitator (PAF). General advice from the GP to patients about physical activity is a common element in health promotion. However, in this trial, patients would only receive the advice of the Physical Activity Facilitator and access to many of the physical activity options if they meet the Physical Activity Facilitator. This is an advantage of the TREAD intervention over one that uses practice staff. In this trial, we do not think that contamination will be a serious problem but we will measure activity levels in both arms as a means of monitoring this aspect.

2b) Recruitment

Recruitment will take place over a 27-month period, predominantly in general practices that are currently part of the well established primary care R & D networks in Bristol (Avon Consortium - 20 practices) and Exeter (PenRen - 40 practices). We will ask GPs to refer patients whom they have just started on antidepressant medication for depression and also depressed patients who are not currently on antidepressant medication but who wish to pursue further treatment for their condition. We will use a variety of means to encourage referral to the trial. These will include stickers, posters, newsletters and other publicity. We will also screen practice computer systems for people who have recently been diagnosed as depressed or given an antidepressant, in order to recruit additional participants who have not been referred by their GP to the trial via consultation.

The two GP research networks we plan to use have a strong track record in carrying out research and both have experience and commitment to mental health trials. We will be providing a well thought out package as the intervention and this will help to gain the confidence of the GPs and encourage recruitment. The GP will ask patients diagnosed with depression if they are interested in taking part in the trial and suggest that they release their personal details to the research team for further contact. Once given permission to contact the patient, a Research Assistant will perform the baseline assessment, confirm eligibility and obtain informed consent. For participants randomised to the intervention arm, an appointment will be made to meet the Physical Activity Facilitator in the general practice, at the research office, or in the patient's home. For those randomised to the control arm, the participant will be asked to continue with their usual GP care.

Blinding and other forms of bias
It is not possible to blind participants or their GPs to their allocation of treatment. As far as possible, we propose to use self-administered measures to assess outcomes, in order to eliminate any observer bias. We have, therefore, chosen not to use clinician-based measures of outcome such as the Hamilton Rating Scale for Depression.[31] We propose to minimise selection bias by recruiting participants from a variety of practices based in rural, urban, affluent and deprived areas. Bristol and Exeter provides a whole range of environments from the deprived and ethnically-mixed inner city of Bristol to market towns and rural areas. We will also aim to keep exclusion criteria to a minimum.

Allocation to trial groups
The study will use individual allocation from a central telephone randomisation service controlled by an administrator in Bristol. Allocation will be stratified by antidepressant use (yes, no), and minimised by severity of depression (CIS-R score of ≤25, 26-33, 34+ at baseline), recruiting centre (Bristol, Exeter) and level of physical activity (≤1, 2-3, 4+ days per week where at least 30 minutes of moderate intensity physical activity is undertaken.) We do not think it is practicable to stratify by practice, age or receipt of psychotherapy since this would then have too many strata for the randomisation. In any case, minimising by centre will ensure balance in terms of local factors including any co-interventions, and will ensure proportionate workload for the Physical Activity Facilitators. Stratification by use of antidepressant medication is justified as this may have an important bearing on the trial outcome as explained above. Minimisation by the other variables will ensure balance between the arms of the study and help with power since these factors, particularly baseline severity of depression, are likely to be important predictors of outcome.

2c) *Planned interventions*

The principles behind the intervention have been described already in Section 1b. We propose to develop an intervention manual, based on the NHS National Quality Assurance Framework for Exercise Referral Schemes (NQAF) and the existing referral scheme in Somerset (in operation for over 10 years) which involves a trained exercise facilitator. The patients in receipt of the intervention will be given a list of local physical activity options, in addition to support from the Physical Activity Facilitator.

Physical Activity Facilitators
Two part-time Physical Activity Facilitators at each site will be required, two each for Bristol and Exeter. They would be graduates of existing undergraduate and MSc courses and would have some practical experience of similar facilitation processes. They will have two days additional training in the nature of depression, pharmacological treatment, characteristics of depressed patients and working in primary care settings. The Departments of Exercise, Nutrition and Health Sciences at Bristol and the School of Sport and Health at Exeter will provide professional supervision, support and resources for their professional development. Each Physical Activity Facilitator will be employed by the relevant academic institution and cover a number of local practices. Physical Activity Facilitators will be instructed not to discuss any non-intervention patients with any other staff in the practice.

Frequency of contact
The goal of the Physical Activity Facilitator is to maximise long-term increases in physical activity over a period of eight months. There would be an initial face-to-face assessment meeting lasting around 45 minutes followed by a series of up to ten further telephone contacts and two further face-to-face 30-minute meetings over the 8-month intervention period. These further contacts would follow a protocol, depending upon whether the person was meeting agreed goals. For example, contacts would be less frequent and intense if the person was successfully implementing the physical activity plan.

Contents of manual
The manual will provide practical guidance on the principles outlines in the introduction. It will also provide a structure for the assessment interview to include physical activity history, motives and barriers to undertaking physical activity as well as scoping patient needs and preferred options. The facilitator would agree an activity plan with the patient and set both short and long-term goals. Simple psychological and behavioural techniques would be described to help people adhere to a physical activity plan, including the use of diaries to record physical activity. Background information about depression would also be provided.

Physical activity advice
The physical activity advice given to participants in the intervention will be individually tailored to take account of current levels of fitness, motivation and previous experience of physical activity. Short-term goals will be tailored to the patient's recent physical activity history with the long-term goal of achieving the recent recommendations[4]; i.e. 30 minutes (in one or more sessions) of moderate intensity activity (e.g. brisk walking) on at least five days each week. The emphasis will be on frequency of daily activity in the first instance, followed by increasing duration of sessions. A recent review of existing trials has shown no difference in adherence to programmes of physical activity using shorter versus long bouts.[29]

Monitoring intervention.
A random sample of the face-to-face and telephone contacts for all Physical Activity Facilitators will be recorded to ensure adherence to the model and consistency of delivery.

Usual care
The usual care group will be advised to follow the current advice of their general practitioner regarding their depression and its treatment.

Loss to follow-up
Our sample size calculation has allowed a 15% loss to follow-up at 4-months post-randomisation. A recent randomised controlled trial conducted by two of the Co-applicants[32] achieved an 81% follow-up rate at 6 weeks. In a recent, mild depression trial (MRC G9304472) we had an 88% follow-up rate at 6 weeks and 81% at 12 weeks. In order to minimise attrition, data collection at 4 and 12-month follow-up will be conducted face-to-face wherever possible.

Acceptability
There are two aspects to the acceptability of the trial. The first is the acceptability of the physical activity intervention. We suspect that some individuals will refuse to consider the trial because they do not like or want to carry out any physical activity. As discussed above, we will ensure, as far as possible, that the intervention is acceptable and individually tailored to the participants and this will be explained by the Research Assistant. The second issue is the acceptability of the randomisation procedure. In the trial, there will be no interference with usual care. The GP and patient can decide on any additional treatments including antidepressants, counselling or referral to secondary care, as they feel appropriate. However, half the people entering the trial will not be randomised to the physical activity intervention. We do not, however, think that this will reduce the overall acceptability of the trial, since it will provide an extra treatment option that is not widely used in the two areas in which the study will be conducted.

2d) *Planned inclusion / exclusion criteria*

We seek to recruit people with mild and moderate depression who are beginning a new episode of depression. We will, therefore, include people aged 18-69 who have either recently started antidepressants (within 4 weeks of their assessment and following an antidepressant free period of at least 1 month) or who are not currently on antidepressants but have recently consulted their GP for depression. The baseline assessment will use the revised Clinical Interview Schedule (CIS-R)[33;33] administered by computer in order to make an ICD-10 diagnosis of depression (F32), a criteria for inclusion in the trial. The participants will also have to score 14 or more on the Beck Depression Inventory[34] (BDI), in order to ensure that there is room for improvement in our primary outcome. Other exclusions will cover any medical contraindications to physical activity[35], inability to complete self-administered questionnaires in English, psychosis, bipolar disorder and any serious drug or alcohol abuse. Women who are pregnant at the time of recruitment will automatically be excluded from the trial but those who become pregnant during the trial may continue, providing they have approval and permission to do so from their GP. We will request consent from patients referred by the GP to use basic demographic information as a means of describing those who are excluded from the trial in comparison with those who do take part

2e) *Ethical issues*

We do not think this trial will raise any particular ethical issues. We are not interfering with the usual clinical care of participants. The physical activity intervention is an extra intervention in addition to GP usual care. We are obtaining valid informed consent from the subjects. The lack of a clear effect of physical activity in the treatment of depression from the most up-to-date systematic review[5] shows that there is clinical equipoise. Finally, participants can still receive antidepressants, counselling or psychotherapy during the course of the trial, if this proves necessary or desirable.

2f) *Proposed baseline and outcome measures*

Primary outcome
The primary outcome will be clinical symptoms of depression assessed using the Beck Depression Inventory (BDI)[34]. In the analysis, BDI will be treated as both a continuous and binary (<10 or ≥10) outcome. The continuous outcome will give a measure of improvement and the binary an estimate of the proportion that has symptomatic recovery. Both are important clinical outcomes and we will power the study to detect differences in both. The primary follow-up will be at 4-months post randomisation as we would expect the maximum impact at 4-months. This corresponds broadly to the time-frame that was used in previous trials[5]. The primary analysis that we, therefore, propose is the BDI score at 4-months, after adjustment for BDI score at baseline.

Secondary outcomes
Other depression and anxiety measures
It is difficult to measure episodes of depression retrospectively, so number of days prescribed an antidepressant during the 12-month follow-up period will be a secondary outcome. This will be measured by searching the GPs' computerised records and by using a self-reported measure of medication adherence. We will also use BDI (both continuous and binary) at the 8 and 12-month follow-ups in order to measure longer term effects of the intervention on our outcomes. The Physical Activity Facilitator will maintain contact with the participant for approximately eight months (though at a reduced level) whilst the 12-month data collection will allow investigation of any longer term sustained effects on outcomes. We will also ask about any depressive episodes between the follow-up times but recognise that this information is likely to be inaccurate.

Quality of life
Quality of life will be assessed using the SF-12[37] at baseline, 4, 8 and 12 months. This is a widely used scale that examines a range of items concerned primarily with functional status. The EQ-5D [38] will also be used in the economic analysis.

Measuring adherence to physical activity programme
We will measure adherence to the physical activity programme at baseline and all follow-up points using a self-reported questionnaire comprising a variety of previously validated and specially drafted measures[39]. Because of the known error in self-reported physical activity, and the need to monitor activity levels in the usual care group, we are proposing the use of accelerometers in a sub-sample of participants. Accelerometers are matchbox-sized computers that are worn, during waking hours, on a belt at the hip. They provide minute-by-minute estimates of movement. This movement can be translated into number of steps walked and percentage of time spent in different intensities of activity. They can also identify sustained sessions of activity at various intensities, including sedentary time and thus providing a comprehensive activity profile. Additionally, movement counts can also produce estimates of energy expenditure[40;41]. These accelerometers will be used to record a week of activity by a random sample of the patients at 4-month follow-up. We will carry out these tests on 50 subjects in each treatment group with the aim of validating the self-reported activity data. This sample size is based upon current advice[42] for reliability testing to give reasonably precise (± 0.15) estimates of the reliability coefficient. It should enable us to detect, at 80% power and 5% significance, a difference of 0.4 SD in the mean activity levels between the two randomised groups.

Other measures
Because of the possible link between physical activity and other psychosocial variables we will measure social support (using ONS Psychiatric survey scales)[43], physical self perceptions[44] and physical activity self-efficacy[45] at baseline and all follow-up points. Personality variables are also very important prognostic indicators and we will, therefore, use the Big Five inventory to investigate these.[46] A discrete choice experiment (DCE) in questionnaire format will also be included, in order to examine patients' preferences for different aspects of the physical activity intervention.

Baseline assessment
This will consist primarily of the CIS-R, BDI, SF-12, EQ-5D, self-report physical activity questionnaire, as well as questions on social support, physical self-perceptions, physical activity self-efficacy, previous psychiatric history and socio-demographics.

2g) Economic data & analysis

The aim of the economic evaluation is to compare the costs and benefits of physical activity in addition to usual care with usual care alone for primary care patients with depression. These two proposed methods of patient care will be compared from the viewpoint of: (i) the National Health Service (NHS) and personal social services (PSS), (ii) patients and carers, and (iii) society[47]. The analysis will be based on the costs incurred over the 12 months following randomisation, measured at baseline, 4, 8 and 12 months.

Resources used by all patients will be identified, measured and valued. The principal costs to the health care provider will relate to the cost of the intervention, primary and secondary health care contacts, and medication. Patients and carers are likely to incur travel costs, use of alternative therapies, loss of income, and home support costs such as childcare. Societal costs will relate to lost production due to time off work. We will collect patient level data from routine sources such as practice records, as well as a patient questionnaire based on the Client Service Receipt Inventory[48], which has been used elsewhere to assess the costs of treating mental illness. This will be adapted to suit this study, this patient group and for postal administration.

Health care resources will be valued using published national sources, for example, Unit Costs of Health and Social Care and the British National Formulary. The cost of the intervention will be based on the cost of its provision in the trial, but any protocol-driven research costs will be excluded. Informal care giving will be valued using the principle of opportunity cost, so the shadow price of informal care will be estimated as the unit cost of a home care worker. In valuing lost production, we will follow the recommendations of Drummond[49]. Productivity losses will be reported separately and measured in terms of days lost. We will estimate the value of lost production using the 'friction' approach, a variation of the 'human capital' approach, which includes only the resources required to replace the employee. Costs and outcomes at 12 months will be discounted at the recommended rate of 3.5%.[49] Costs will be related to the primary clinical outcome of the trial (BDI) and quality of life as measured by the EQ-5D.[38]

It is our intention that incremental cost-effectiveness ratios will be formed comparing (i) the cost per extra patient recovering; (ii) the cost per depression free days; and (ii) the cost per QALY gain, for each of the proposed treatments. Sensitivity analyses will be conducted in those areas where there is uncertainty around assumptions about resource use measurement and/or valuation. Patient variation in resource use and the effectiveness of the intervention will be captured using 'bootstrapping' to construct a cost effectiveness acceptability curve.[50]

2h) Feasibility Phase

Aims of feasibility phase
Given the novelty of the trial, we propose carrying out a feasibility phase study in order to:

- estimate recruitment rate
- pilot and refine physical activity intervention
- investigate acceptability of the recruitment procedure and physical activity intervention.

1) estimate recruitment rate
In our original proposal, we estimated our recruitment rate as 2.5 participants per practice per month, using a 12-month recruitment period. If we extend the recruitment period by 3 months, the required recruitment rate drops to 2 per practice per month. We are currently recruiting for a trial of antidepressants in depression (GenPod MRC G0200243) and initial impressions are that it is realistic to recruit at that rate. However, we recognise that this is a challenging recruitment rate and its achievement will depend upon how potential recruits view the acceptability of the physical activity intervention. The feasibility phase will, therefore, provide us with a more precise estimate of the recruitment rate to this trial.

2) pilot and refine physical activity intervention
The physical activity intervention will be piloted and refined during the feasibility phase. As we have argued, a physical activity intervention for people with depression has somewhat different requirements to a generic physical activity intervention. Though we have already given a very clear idea of these requirements, an extended developmental phase would be valuable since it will allow the Physical Activity Facilitators to gain experience of delivering the intervention before the main phase of the trial starts. One element of this work will be to create a local list, for both the Bristol and Exeter sites, of community-based physical activity opportunities that are not provided in local leisure centres.

3) investigate acceptability of the recruitment procedure and physical activity intervention
We will additionally investigate the acceptability of the recruitment procedure and the physical activity intervention using qualitative methods. This will provide more systematic evidence with which to revise the recruitment process and the intervention. In-depth interviews will be carried out with participants, practice managers, general practitioners (GPs) and key trial personnel such as the Trial Co-ordinator, Research Assistants and Physical Activity Facilitators. We will also invite potential participants who have refused to take part in the randomised trial to be interviewed, although we recognise that they may be reluctant to take part in the qualitative interviews. The interviews with GPs, practice managers and participants will focus upon their experience of recruitment and the perceived acceptability of the recruitment process as well as considering their own views about clinical equipoise in relation to the trial. We will ask them to describe the reasons why they decided to take part (or not if more appropriate) and how they weighed up the advantages and disadvantages of doing so.

For participants allocated to the intervention arm, we will also ask them about physical activity. We will attempt to interview anyone who drops out of the physical activity treatment arm as well as those who continue with it. The interviews will focus on the reasons behind their decision to continue or stop the physical activity intervention as well as exploring those aspects they found most and least helpful. The Trial Co-ordinator would carry out the recruitment for individuals who would then be interviewed using qualitative methods by the Research Assistant. Interviews will be carried out with approximately 4 GPs, 2 practice managers and up to 12 participants, unless the results indicate that further interviews are required. All interviews will be audio-taped and transcribed. Data collection and analysis will run in parallel. Transcripts will be studied in detail and a list of common themes and concepts drawn up. The analysis of the data will follow the principles outlined in the main trial methods section. The resulting data will enable us to modify the recruitment method and, if necessary, the intervention.

2i) Sample size justification

Our original power calculation anticipated that about 60% of participants in the usual care group and 73% in the intervention group would have recovered by 4-month follow-up – scoring <10 on the BDI. This difference of 13% in the proportion 'recovered', equivalent to an odds ratio of 1.8, is consistent with the lower end of treatment effects observed with antidepressant medication, but is still substantial and worth detecting for a common condition such as depression and for an intervention with other possible health benefits such as physical activity. With 90% power and 5% two-sided alpha, this would require 291 patients per group.

When using the BDI as a continuous outcome, previous studies have estimated a standard deviation of about 9 points[51], and have suggested that a worthwhile and feasible target difference is about 3-4 points. With 5% two-sided alpha, a sample size of 291 per group will afford 98 to >99% power to detect a difference of 0.33 to 0.44 standard deviations. Furthermore, it will yield a derived margin of error for the difference between the randomised groups of approximately 0.16 standard deviations, equivalent to 95% confidence intervals on the BDI scale of approximately 1.5 to 4.5 and 2.5 to 5.5 for estimated differences of 3 and 4 respectively.

The table below presents original estimates for numbers required to be recruited for different powers and proportions of patients not on antidepressants at baseline, allowing for an attrition rate of 15%, and based on detecting an odds ratio of 1.8 with 5% two-sided alpha.

power	% untreated at baseline			N for analysis	derived margin of error for primary comparison
	0%	5%	10%		
80%	520	548	578	442	1.68
85%	592	622	658	502	1.57
90%	686	722	762	582	1.46

Assuming that 10% of the sample would not be on antidepressant treatment when recruited, and that, overall, there would be a 10-15% attrition rate, the sample size specification above required 291 per group to be available for analysis. In order to achieve this, the total number that will need to be recruited, depending on the attrition rate, would be between 720 and 762 [(291*2)/(0.9*0.9) to (291*2)/(0.9*0.85)]. We, therefore, proposed to recruit 762 participants at the outset.

However, our initial calculation made a number of assumptions about:

- recruitment rate
- antidepressant use
- recovery rate at 4-month follow-up
- follow-up rate

Recruitment rate
In our original proposal, we predicted that we could randomise two participants per practice per month. In fact, the recruitment rate achieved in the first few months of the trial was far lower, at around 0.3 participants per practice per month or approximately 18 participants per month for each of the 60 practices we initially planned to recruit. As a result, it became clear that we were unlikely to meet our original recruitment target within the original timeframe. Indeed, if we continued to recruit to the original schedule, we would only expect to recruit between 180 and 198 participants overall. However, if we extend recruitment by an additional twelve months, and assume the same recruitment rate of between 15 and 18 per month, we would expect to recruit between 360 and 414 participants in total.

Antidepressant use
Originally, we were concerned that patients not on treatment i.e those allocated to the usual care arm, were more likely to be prescribed antidepressants during the trial and that this might lead to a marked reduction in any expected treatment effect. We anticipated, at the outset, that the proportion of patients not on treatment would be approximately 10% of those recruited. We, therefore, proposed to power the study and conduct the primary and main secondary analyses on the 90% of recruited patients who we anticipated would be on antidepressant treatment at the point of randomisation. However, data from the early stages of the trial suggests that about 50% of randomised patients were taking antidepressants. On this basis, and taking into account the fact that randomisation is stratified by antidepressant use at baseline, we are reassured that we should include all randomised participants in the primary analysis, irrespective of antidepressant use. .

Recovery rate at 4-month follow-up
The original power calculation had assumed that 60% of participants would recover within four months. However, the proportion of patients seen to recover in the recently concluded IPCRESS study was found to be somewhat lower, with only 20% of participants recovering in the waiting list group (19/92 = 20.6%; 95%, CI 12.9-30.3). Our revised power calculations, therefore, examine the difference between 20% and 33%, maintaining the original absolute difference in rates from our original power calculation. This will not have any effect on the estimates of precision in relation to continuous outcomes.

Follow-up rate
In the original protocol, we had assumed an 85% retention rate at 4-month follow-up i.e. our primary outcome. Rate of follow-up is difficult to estimate accurately but current confidence limits do include this value. We are, therefore, confident that we can meet our target of 85% and have continued to use this assumption in our revised power calculations. Our original protocol outlined postal follow-up at 4-months but other studies have shown that collecting follow-up data in person can improve follow-up rates. We, therefore, propose to carry out both the 4-month and 12-month assessments in face-to-face mode wherever possible.

The table below provides a summary of our revised power calculations assuming a 27-month recruitment period. We have given figures for both our most conservative estimate of recruiting fifteen randomised patients per month and a more optimistic upper bound of recruiting eighteen randomised patients per month. We conclude that the revised sample size will still give us adequate power for our primary analysis using the continuous outcome. Whilst there will inevitably be some reduction in power for the categorical outcome, we will still be able to detect a 14% or 15% difference with 80% power.

monthly recruitment rate	total N randomised	N for primary analysis	power for 73% vs 60% (OR = 1.80)	power for 20% vs 33% (OR=1.97)	detectable difference with 80% power[1]	error factor[2] for odds ratio	power to detect 3 BDI point difference	standard error[3] on BDI
15	360	306	63%	69%	15%	1.68	82%	1.03
18	414	354	70%	76%	14%	1.62	87%	0.96

[1] percentage difference of intervention from usual care assuming recovery in usual care is 20%
[2] error factor = 1.96 * SE (log odds ratio)
[3] assuming BDI standard deviation of 9

2j) Statistical analysis

The analysis and presentation of this pragmatic randomised trial data will be in accordance with CONSORT guidelines[53], with the primary comparative analyses being conducted on an intention-to-treat basis and due emphasis placed on confidence intervals for the between-arm comparisons. Descriptive statistics of socio-demographic and clinical measures will be used to detect any marked imbalance between the arms at baseline. As described previously, we intend to make full use of BDI as both a binary and continuous outcome measure in the interpretation of the results of this trial. Although unusual we, therefore, specify two primary analyses. These primary comparative analyses will employ multivariable logistic or linear regression, as appropriate, to investigate differences between the groups, adjusting for minimisation variables and baseline BDI amongst those medicating at baseline. For the binary outcome, the comparison will be presented as an odds ratio of recovery (scoring <10 on the BDI) in the intervention group compared with the control group. For BDI as a continuous measure, the comparison will be presented as a difference in group mean scores. For both outcomes we will also present 95% confidence intervals and p-values.

Sensitivity analyses, making different assumptions such as 'best' and 'worst' case scenarios as well as imputation models of 'missingness', will be conducted to investigate the potential impact of missing data. We will also investigate the extent and impact on the results of clustering by general practice and possibly Physical Activity Facilitator; although the small number of facilitators will mean that investigation of such effects will be limited. In the absence of adequate power to formally test for differential effects according to antidepressant therapy at baseline, we will investigate the patterns of confidence intervals for both subsets of patients separately and combined.

In addition to carrying out the same analyses for the secondary outcomes (where p-values will be adjusted to account for multiple testing), and to repeating any such primary analyses adjusted also for any variables exhibiting marked imbalance at baseline, the secondary analyses for this trial will take three general forms:

a) investigation of process measures such as adherence to the physical activity programme, use of antidepressants, counselling and social support. Mostly these will be descriptive analyses, but this information will be used to investigate whether adherence to the physical activity programme is associated with 'recovery', and will also be employed within the economic evaluation.

b) some of this process data will also be employed in secondary, explanatory analyses that attempt to explain the comparisons between the two treatment arms from the intention-to-treat analyses. This will be investigated by adjusting for factors such as adherence to the physical activity programme in the intervention group, but also reported activity levels in both groups. The models employed will be essentially the same as those for the primary analyses. In addition, we will investigate the patterns of BDI scores (as a continuous measure) between the groups at the 4, 8 and 12- month follow-up using repeated measures (random effects) linear regression, adjusting for baseline BDI, minimisation factors, and any other variables displaying imbalances at baseline. Divergence or convergence between the two groups over time will also be investigated using appropriate interaction terms.

c) thirdly, appropriate interaction terms will be entered into the primary regression analyses for BDI as both a binary and continuous outcome. in order to conduct pre-specified subgroup analyses according to baseline severity of depression (CIS-R score of ≤25, 26-33, 34+ at baseline) and baseline physical activity level (≤1, 2-3, 4+ days per week where at least 30 minutes of moderate intensity physical activity is undertaken.) Since the trial is powered to detect overall differences between the groups rather than any interactions terms, the results of these exploratory analyses will be presented using confidence intervals as well as p-values, and interpreted with due caution.

2k) Qualitative Study

Qualitative methods can be an essential part of a trial's evaluation and can provide another perspective on a trial's results from those provided by the quantitative analysis. Within TREAD, results from a qualitative study could help us understand why the physical activity intervention, in addition to usual GP care, was or was not effective in changing the outcome of depression and/or altering subsequent use of antidepressants. We, therefore, suggest that the qualitative work is not restricted to the feasibility phase of the trial but also extends into the main trial.

The main aim of the qualitative study will be to explore patients', health professionals' and Physical Activity Facilitators' views and experiences of the physical activity intervention, in order to assess its acceptability and to illuminate possible reasons for the quantitative results. Study objectives are to:

- assess patients' views and experiences of the physical activity intervention
- identify patients' reasons for accepting, declining, adhering to or withdrawing from the intervention
- explore health professionals' views of the intervention and its impact on general practice
- assess the Physical Activity Facilitators' views and experiences of providing the intervention

Design
We intend to carry out the qualitative study in practices that are already participating in the main trial, with access to the same intervention and the same Physical Activity Facilitators. However, since in-depth qualitative interviews have some similarities to supportive counselling, we propose to only interview trial participants after they have provided follow-up data on the primary outcome, in order to avoid unduly influencing the main trial. The qualitative study will entail conducting interviews with trial participants, health professionals and the Physical Activity Facilitators. It will also involve recording patients' reasons for declining to take part in the trial and for not adhering to the intervention.

Interviews with trial participants
Using information collected during the baseline questionnaire, participants will be purposively sampled to ensure that interviews are held with men and women of varying age, who differ in terms of what their level of physical activity had been at baseline (i.e. low, medium or high). Within this sampling approach, we will also aim for maximum variation in relation to level of depression, history of depression, socio-economic background, and whether individuals live in rural or urban areas. Interviews will be carried out with trial participants recruited in both Bristol and Exeter, and in both arms of the trial.

All participants taking part in the trial will have consented at baseline to being approached by a qualitative researcher. Thus, the researcher employed to conduct the interviews will telephone individuals who have been sampled for the qualitative study to ask if they would be willing to take part in an interview. The researcher will explain the aims and design of the qualitative study and answer any questions the participant might have. If the participant is willing to take part in an interview, an interview time and place will be arranged. A letter confirming the interview arrangements will then be posted to the participant. This letter will be accompanied by an information leaflet about the study.

Participants will be interviewed on two occasions: within a month of the 4 month follow-up and at 12 months post-randomisation, i.e. once the primary and final outcome measures have been completed. The interviews will take place at a time that suits the individual, at a location of his/her choice. Prior to interview, both written and verbal consent to be interviewed will be secured from the participant.

The four-month interview with participants in the intervention arm will explore their reasons for taking part in the trial; their views about physical activity as a treatment for depression; what physical activity they were undertaking prior to TREAD; their experiences of the intervention; their relationship with their Physical Activity Facilitator; their experiences of usual care and what other treatments they have tried or are using for their depression; barriers and supports to increasing levels of physical activity; how they think their views towards physical activity have changed; how they think physical activity has affected their depression; and whether or not they think physical activity has become more integrated into their lives. Participants in the control group will also be asked about their reasons for taking part in the trial, their views on physical activity as a treatment for depression and what physical activity they were undertaking prior to TREAD. In addition, they will be asked about their experiences of usual care and what treatments they have used to manage their depression.

The twelve-month interview with participants in the intervention arm will explore their experiences in the later stages of the intervention; whether or not they have managed to maintain changes made whilst in contact with a Physical Activity Facilitator; and what factors have supported or prevented further changes or changes being maintained. Interviews with those in the control group will assess their experiences of usual care and what treatments they have used to manage their depression.

Data collection will continue until saturation of key themes has been reached. It is predicted that this will mean about 50 individuals will be interviewed in total, i.e. 20 from the control group and 30 from the intervention group. Interviewing about 50 individuals at the 4-month point will also ensure that we have adequate numbers of participants at 12-months post-randomisation to make this second data set meaningful.

Recording of reasons for declining to take part in the trial
Patients who have agreed to have their contact details passed on to the research team may still decline to take part in the trial. They may decline on being contacted by the research team or at the baseline assessment prior to randomisation. It is important that we explore why individuals decline to take part in the trial, as these individuals may have specific views towards physical activity as a treatment of depression, particularly in terms of its acceptability and effectiveness. Thus, in situations where an individual declines to take part in the trial, the researcher conducting the initial telephone 'screen' or baseline assessment will invite him/her to explain his/her decision. Any reasons given will be noted.

Recording of reasons for withdrawing from the intervention
Some participants randomised to the intervention arm may decide not to continue with the intervention. Like the individuals who decline to take part in the trial, these individuals may hold particular views toward the intervention and, therefore, provide important insights into its acceptability. Where possible, the Physical Activity Facilitator or researcher in touch with these individuals will invite them to explain the rationale behind their decision to discontinue treatment. Any reasons given will be noted.

Interviews with health professionals
Interviews will be held with GPs who have been involved with the trial. We will sample GPs in both Bristol and Exeter, GPs who have and have not referred to the trial, and GPs working in areas of varying levels of affluence/deprivation and urbanisation. GPs sampled will be sent a letter inviting them to take part in an interview. This letter will be accompanied by an information sheet. The qualitative researcher will then telephone or email the GP a week later to ask if s/he would be willing to take part in an interview. To encourage participation, GPs will be given the choice of being interviewed at their place of work, at home or over the telephone. The interviews will explore GPs' views on physical activity as a treatment for depression, their use and implementation of the physical activity programme, their views on its impact on general practice, and their reasons for referring or not referring patients to the trial. GPs who did refer patients will also be asked about which patients they referred to the study and any information they have on why patients had refused to take part. These interviews will be held once recruitment to the trial has ended.

It is predicted that about 10 to 15 GPs will be interviewed in total. Prior to interview, both written and verbal consent to take part in an interview will be secured. In practices where others have been involved with the recruitment process, e.g. Practice Managers, once recruitment to the trial has ended, interviews will also be held with these professionals to explore their views on physical activity as a treatment for depression. These individuals will be invited and consented for interview using the same approach and paperwork used for recruiting GPs. It is predicted about 5 such interviews will be held.

Interviews with Physical Activity Facilitators
The Physical Activity Facilitators in both Bristol and Exeter will be asked to take part in an interview, once they have finished delivering the intervention. The qualitative researcher will explain to them that the purpose of the interview will be to explore their views and experiences of delivering the intervention, their understanding of the aims of the intervention and the rationale behind its design, and how they translated key elements in to practice. The researcher will also provide the Physical Activity Facilitators with an information leaflet that provides more details about the interviews. The researcher will then contact each Physical Activity Facilitator a week later to ask if she would be willing to take part in an interview. The interviews will take place at a time that suits the facilitator, at a location of her choice. Prior to interview, both written and verbal consent to take part in an interview will be secured.

Data analysis
With participant consent, all the interviews will be audio-taped, fully transcribed and anonymised. Notes taken by members of the research team about reasons for declining or not adhering to the intervention will also be typed up. Data collection and analysis will run in parallel. Transcripts will be read and re-read in order to gain an overall understanding of each interviewee's views and experiences. This process will also be used to develop a coding frame, to identify common themes and concepts. The coding frame will be developed and refined as additional material emerges. Each transcript will be imported into a software package, such as ATLAS.ti, to allow electronic coding and retrieval of data. Transcripts will be coded by two independent researchers in order to maintain reliability of coding. The analysis will rely upon "constant comparison" and will continue until no new themes emerge. Data collected from trial participants might also be analysed using a biographical approach so that we can identify developments between the first and second interview, in terms of behavioural changes, participants' knowledge and attitudes.

2l) Management and supervision of trial

Many of the Bristol Co-applicants are based in the Department of Community based Medicine at Bristol University (GL, DS, TP, NW, AM, SH) whilst the Department of Exercise, Nutrition and Health Science (KF, AH) is a on the same University precinct, as is the Department of Social Medicine (MCal, DL). Exeter (JC, AT) is 75 minutes drive from Bristol, with regular train services between the two cities. We will have a full-time Trial Co-ordinator based in Bristol who has overall responsibility for the trial. The Trial Co-ordinator will develop the detailed protocol, finalise baseline and follow-up assessments, manage the Research Assistants, maintain the central database and coordinate meetings of the management group and Trial Steering Committee. They will also take the lead in the data analysis and preparation of final reports with the assistance of the Co-applicants when needed. A number of Research Assistants will be based in both Bristol and Exeter. Their primary role will be to conduct baseline assessments, obtain consent and activate the randomisation procedure. The administrators will arrange appointments and send out the mailings for follow-up assessments, working alongside the Research Assistants, for the Trial Co-ordinator. A research management group comprising GL, NW, JC, AM, SH, the Trial Co-ordinator, Research Assistants and administrators will meet monthly. KF, AH, AT, DL will attend regular meetings, when required, to supervise the physical activity element of the trial. A Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) will be appointed based upon MRC guidelines and after approval from the HTA.

The Co-applicants are all in WestHub, part of the Mental Health Research Network (MHRN). The study will be adopted by both the MHRN and PCRN and this will give us access to the infrastructure to help with ethics applications, research governance and recruitment. The study will also benefit from the experience gained from existing HTA and MRC treatment trials of depression in Bristol.

3. PROJECT TIMETABLE and MILESTONES

The original timetable has been modified to include delays to the start-up of the study. The final study schedule is shown below:

Timetable: 5 years, 3 months

0-9 months:	Secure MREC and NHS research governance approval. Recruit staff.
10-14 months:	Begin recruiting practices. Develop protocol, questionnaires and SOPs.
15-21 months:	Conduct feasibility phase. Finalise protocol. Continue recruiting practices.
22 months:	Start of main trial. Begin to recruit patients. Carry out baseline assessments.
26 months:	Begin 4-month follow-up assessments.
30 months:	Begin 8-month follow-up assessments.
34 months:	Begin 12-month follow-up assessments.
39 months:	Start of qualitative component.
54- 56 months:	Extract GP computer record data.
57-61 months:	Conduct data analysis.
62-63 months:	Prepare final report.

4. EXPERTISE

The study team has psychiatry (Glyn Lewis), physical activity (Ken Fox, Adrian Taylor, Anne Haase, Debbie Lawlor) primary care (Debbie Sharp, John Campbell, Debbie Lawlor) randomised clinical trial (Glyn Lewis, Debbie Sharp, Tim Peters, Alan Montgomery, Nicola Wiles, Debbie Lawlor, Melanie Chalder), statistical (Tim Peters, Alan Montgomery), health economics (Sandra Hollinghurst) and qualitative (Mike Calnan, Adrian Taylor, Katrina Turner) research expertise. Anne Laure-Donskoy, a member of our local service user group SURF has contributed to the proposal and a number of other lay members have been involved in the drafting of the trial documentation and management. We will make use of two well-established and active primary care research networks based in Bristol and Exeter. We have recently completed three randomised controlled trials of depression funded by the MRC, HTA and BUPA Foundation in Bristol and this study will also benefit from the management experience of our well-established Trial Co-ordinators group. The Department of Exercise, Nutrition and Health Science in Bristol has participated in three randomised trials of physical activity / exercise for other health related conditions.

5. DISSEMINATION

The results will be published in peer review journals and presented to the relevant conferences, nationally and internationally. The production of a manual for the physical activity intervention will enable us to provide specific guidance on the training that would be needed and the nature of the intervention, if it proved cost-effective.

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