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Health Technology Assessment Programme
tel: +44(0)23 8059 5586
email: hta@hta.ac.uk

National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre

University of Southampton, Alpha House
Enterprise Road, Southampton, SO16 7NS
fax: +44(0)23 8059 5639
web: www.hta.ac.uk

Warwick Medical School
CLINICAL TRIALS UNIT

PROTOCOL

ACtive Treatment for Idiopathic AdolescenT Scoliosis (ACTIvATeS): a pilot randomised controlled trial

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Names and contact numbers of ACTIvATeS study team:

Study Lead
Dr Mark Williams
Research Fellow
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
02476574648
Email: m.a.williams.3@warwick.ac.uk

Sponsor
Dr Peter Hedges
Director of Research Support Services
The University of Warwick
Kirby Corner Road
Coventry CV4 8UW
Tel: 024 7652 3859
Email: P.A.Hedges@warwick.ac.uk

Chief Investigator
Professor Sallie Lamb
Director
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
Tel: 024 7657 4658
Email: s.lamb@warwick.ac.uk

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National Institute of Health Research
Health Technology Assessment Agency

http://www.hta.ac.uk/

Co-applicants
Dr Karen Barker
Director of Therapy Research
Nuffield Department of Orthopaedics
Rheumatology and Musculoskeletal
Nuffield Orthopaedic Centre NHS Trust
Windmill Road
Oxford OX3 7LD
Tel: 01865 738080
Email: Karen.Barker@noc.nhs.uk

Professor Jeremy Fairbank
Consultant Spinal, Orthopaedic and Trauma Surgeon
Nuffield Department of Orthopaedics
Rheumatology and Musculoskeletal
Nuffield Orthopaedic Centre NHS Trust
Windmill Road
Oxford OX3 7LD
Tel: 01865227374
Email: jeremy.fairbank@ndorms.ox.ac.uk

Mr Ian Harding
Consultant Orthopaedic Surgeon
Frenchay Hospital
North Bristol NHS Trust
Frenchay Park Road
Bristol BS16 1LE
Telephone: 0117 340 3744
Email: Ian.Harding@nbt.nhs.uk

Dr Anne-Marie Slowther
Associate Professor Clinical Ethics
Warwick Medical School
The University of Warwick
Gibbet Hill Road,
Coventry CV4 7AL
Tel: 02476 574513
Email: annemarie.slowther@warwick.ac.uk

Dr Mark Williams
Research Fellow
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
02476574648
Email: m.a.williams.3@warwick.ac.uk

Mr Peter Heine
Research Fellow
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road,
Coventry CV4 7AL
Tel: 02476150989
Email: p.heine@warwick.ac.uk

Dr Francine Toye
Research Physiotherapist
Physiotherapy Research Unit
Nuffield Orthopaedic Centre NHS Trust
Windmill Road
Oxford OX3 7LD
Tel: 01865738080
Email: Francine.Toye@ouh.nhs.uk

Dr Esther Williamson
Research Fellow
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
Tel: 02476151665
Email: e.m.williamson@warwick.ac.uk

Dr Ranjit Lall
Trial statistician
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
Tel: 02476 574649
Email: r.lall@warwick.ac.uk

Prof Stavros Petrou
Health Economist
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
Tel: 02476 151124
Email: s.petrou@warwick.ac.uk

Dr Neil Coulson
Associate Professor in Health Psychology
Faculty of Medicine and Health Sciences
Level B, International House
Jubilee Campus
Nottingham NG8 1B
Tel: 0115 846 6642
Email: neil.coulson@nottingham.ac.uk

Specialist collaborators

Steve Bunce
Clinical Specialist Physiotherapist
Frenchay Hospital
North Bristol NHS Trust
Frenchay Park Road
Bristol BS16 1LE

Anne Richards
Clinical Specialist Physiotherapist
Nuffield Orthopaedic Centre NHS Trust
Windmill Road
Oxford OX3 7LD

Mr Adrian Gardner
Orthopaedic surgeon
Royal Orthopaedic Hospital
Bristol Road South
Birmingham B31 2AP

Independent monitoring committee

Chair:
Sally Kerry
Research Design Service London - Research Adviser
Reader in Medical Statistics
Centre for Primary Care and Public Health
Blizard Institute
Barts and The London School of Medicine and Dentistry
Yvonne Carter Building
58 Turner Street
London E1 2AB
Tel : 020 7882 7208
Email: s.m.kerry@qmul.ac.uk

Mr Jayesh Trivedi
Consultant Orthopaedic Surgeon
Head of the Department of Spinal Studies
Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust
Oswestry SY10 7AG
Tel:01691404088
Email: Glenys.Hope@rjah.nhs.uk (secretary)

Dr Stephanie Clark (Chair of SAUK)
supported by Sarah Wiles (Communications Manager) and Laura Counsell (General Manager)
The Scoliosis Association (UK)
Unit 4 Ivebury Court
325 Latimer Road
London W10 6RA
Tel: 0208 964 5343
Email: sarah.wiles@sauk.org.uk
laura.counsell@sauk.org.uk

Dr Alison Rushton
Senior Lecturer in Physiotherapy
School of Health and Population Sciences
College of Medical and Dental Sciences
52 Pritchatts Road
University of Birmingham
Edgbaston
Birmingham B15 2TT
Tel: 0121 415 8597
Email: a.b.rushton@bham.ac.uk

Randomisation

Tel: 024 765 150402 (Mon-Fri, 9am to 5pm)
Fax: 024 765 150549

Contents

List of Abbreviations

AIS Adolescent Idiopathic Scoliosis

AE Adverse Event

CONSORT Consolidated Standards of Reporting Trials

CI Chief Investigator

CRF Case Report/Record Form

GCP Good Clinical Practice

HTA Health Technology Assessment

ICH International Conference on Harmonisation

ISRCTN International Standard Randomised Controlled Trial Number

MRC Medical Research Council

QOL Quality of Life

R&D Research & Development

REC Research Ethics Committee

RCT Randomised controlled trial

SAE Serious Adverse Event

SEAS Scientific Exercises Approach to Scoliosis

SOP Standard Operating Procedure

TMG Trial management group

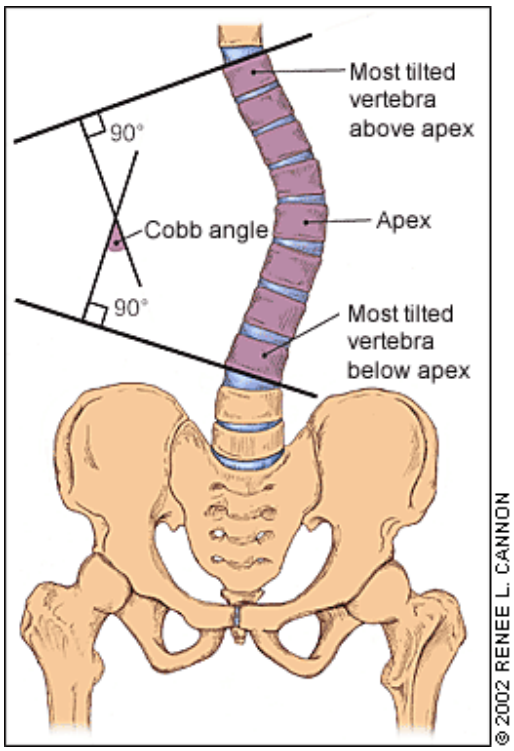
WCTU Warwick Clinical Trials Unit

1 Background

1.1 Epidemiology and burden of condition

Adolescent Idiopathic Scoliosis (AIS) is often referred to as a structural lateral curvature of the spine, although, it is actually a 3 dimensional spinal deformity that results in lateral deviation, rotation and flexion/extension of the vertebrae. It is of unknown cause that occurs at or near the onset of puberty(Lonstein 2006). AIS is commonly diagnosed using the Cobb Angle and to meet the definition the lateral curvature must have a Cobb angle of greater than 10 degrees. A Cobb angle is measured using standing postero-anterior radiographs of the full spine and assesses the lateral curvature of the spine. To do this the most tilted vertebrae above and below the apex of the curve is identified. The angle between intersecting lines drawn perpendicular to the top of the top vertebrae and the bottom of the bottom vertebrae is the Cobb angle (See Figure 1).

Figure 1 Measurement of Cobb Angle



The prevalence of AIS in children aged 10-16 years is 1-3% (Parent, Newton and Wenger 2005, Kesling and Reinker 1997), implying 50,000 - 150,000 sufferers in the UK (Office 2009). The effects of AIS include pain, cosmetic concerns, functional limitations, cardio-respiratory problems and possible further curve progression in adulthood (Weinstein et al.

2003). About 10% of AIS cases require surgical or active conservative management (UK 2010). Current UK management includes monitoring, bracing for some and, for the most progressive and serious cases, surgery. Surgery is generally only undertaken when spinal curvature reaches a Cobb angle >45-50 degrees (Weinstein et al. 2008). Surgery is a very extensive procedure, with exposure of large segments of the spine and substantial fixation which, whilst reducing curve progression, also permanently limits mobility in the affected part of the spine. Surgery also comes with a risk of complications estimated to occur in approximately 6% of patients undergoing spinal fusion for scoliosis and include pulmonary complications, wound infection and neurological damage (Coe et al. 2006).

1.2 Existing knowledge

Currently, the main components of conservative management of scoliosis in the UK are bracing and watchful waiting. Braces are an intrusive and uncomfortable intervention. Two recent publications reported bracing protocols that lasted up to four years and required the brace to be worn for 23 hours per day (Wong et al. 2008, Nachemson and Peterson 1995). The effectiveness of bracing protocols is unclear (Negrini et al. 2010). Exercise is a promising intervention for which there is an emerging, although low quality, evidence base (Negrini et al. 2008, Fusco et al. 2011). The rationale is to use exercises that promote spinal re-alignment, and hence to either improve or halt progression of the curvature. Exercise is potentially a low cost intervention and, even if not effective in all, it would be of substantial benefit if the relative risk reduction in progression to curvature of greater than 45 degrees, or requirement for surgery was reduced in a modest proportion of those participating. It is thought that exercise should be applied as early in the disease process as possible.

Exercise therapy is less commonly provided in the UK and USA, although it is routinely used in Europe (Romano et al. 2010). Within Europe, there are various schools of exercise therapy for AIS. The Schroth method (originating in Germany), Scientific Exercises Approach to Scoliosis (SEAS, Italy), and the Dobomed (Poland) are amongst the most well-known and reported in the literature. However, there is little evidence to support the choice of one over another, or to provide evidence of effectiveness.

The rationale for exercise to manage AIS is that a number of underlying impairments in spinal muscular function and postural ability contribute to or accompany the development of curvature, and are potentially reversible. Electromyography (EMG) of trunk muscles in AIS patients indicate disrupted patterns of muscle recruitment under static and dynamic conditions, in a broad range of postures. These asymmetries extend to the paraspinal lumbar and abdominal oblique muscles, and are associated with a disparity in trunk isometric rotation strength between sides (Avikainen, Rezasoltani and Kauhanen 1999, Mooney, Gulick and Pozos 2000, McIntire et al. 2007, McIntire et al. 2008). In keeping with differential muscle activity, there are differences in muscle fibre-type distribution on the convex and the concave side of the curve. AIS patients exhibit greater balance control problems and proprioceptive impairments (Simoneau et al. 2006, Bruyneel et al. 2010). AIS may be associated with distorted body schema resulting in a mismatch between actual body alignment and patients' internal bodily representation of the body (Smania et al. 2008).

Hence to improve function and reduce/stabilise curvature the exercise programmes must include strengthening of all affected muscle groups, exercise to encourage the appropriate magnitude and timing of muscle activation, proprioceptive elements and postural/body awareness components. The programme will require careful tailoring to each individual. There is evidence that such approaches can remediate underlying impairments in EMG activation and strength, although effects may well be limited to curves with a Cobb angle of less than 50 degrees (Weiss 1993, Schmid et al. 2010, Mooney et al. 2000, McIntire et al. 2007, McIntire et al. 2008).

Although there is a theoretical basis for exercise in AIS, there is little robust evidence that there is a significant effect on curve progression. There are relatively few studies investigating this important outcome (Negrini et al. 2008), and only one randomised controlled trial (RCT). Wan et al (Wan, Wang and Bian 2005) recruited 80 participants with double curves (mean age 15 yrs, SD 4; 43 female, 37 male) and randomised them to either a control treatment or a 6 month exercise programme that targeted impairments of strength and neuromuscular activation. All participants received electro-stimulation therapy and postural retraining. Curve progression was halved in the exercise group (15^{o} v 7^{o}, $p<0.01$) but the quality of the trial was poor. There is no information on cost-effectiveness of the various approaches and whether they offer a viable alternative to surgery and bracing. The exercise approach used in this study differs greatly from the general consensus within Europe where exercises are used routinely as treatment for AIS. A small number of prospective cohort studies have attempted to evaluate the European schools of exercise including SEAS and Schroth (Negrini et al. 2008). Although these studies show a favourable outcome in support of exercises, the research is problematic due to a variety of reasons. These include a lack of control group, failure to randomise, the reporting of very small statistically significant but not necessarily clinically important differences in Cobb angle, poor statistical analysis, limited descriptions of baseline characteristics of participants, adherence to treatment and the exercise programmes evaluated (Mordecai and Dabke 2011). Clear evidence that these approaches are beneficial is currently lacking.

1.3 The need for a pilot trial

A high quality RCT is needed to assess the effectiveness of exercises for patients with AIS. The ultimate aim of this pilot study is, if feasible, to progress to such an RCT which would demonstrate definitively whether or not exercise is clinically and cost effective in AIS management. We estimate that a definitive RCT will require in the region of 400-500 participants (power calculations are in Section 3.7.1). This presents several challenges and is the reason that a pilot study is required before carrying out a full RCT. AIS is a relatively rare condition, and we will require commitment from a substantial proportion of the specialist centres managing AIS in the UK. We need to ensure that there are sufficient numbers of cases who can potentially benefit from the treatment and are willing to participate. The clinicians managing these cases will need to have confidence in the alternative treatments delivered within an RCT to ensure they are willing for patients to be randomised. We also need to maximise the chance that exercise can be effective, not only

by selecting the optimal prescription of exercise, but designing an intervention that encourages compliance. The assumptions underlying the sample size calculation and estimates of recruitment rates also need to be examined.

1.4 Good Clinical Practice

The trial will be conducted in full conformance of the principles of the "Declaration of Helsinki" (1964) (as amended in Tokyo, Venice, Hong Kong, South Africa and Scotland), the Medical Research Council (MRC) Good Clinical Practice Guidelines, and applicable UK legislation.

1.5 CONSORT

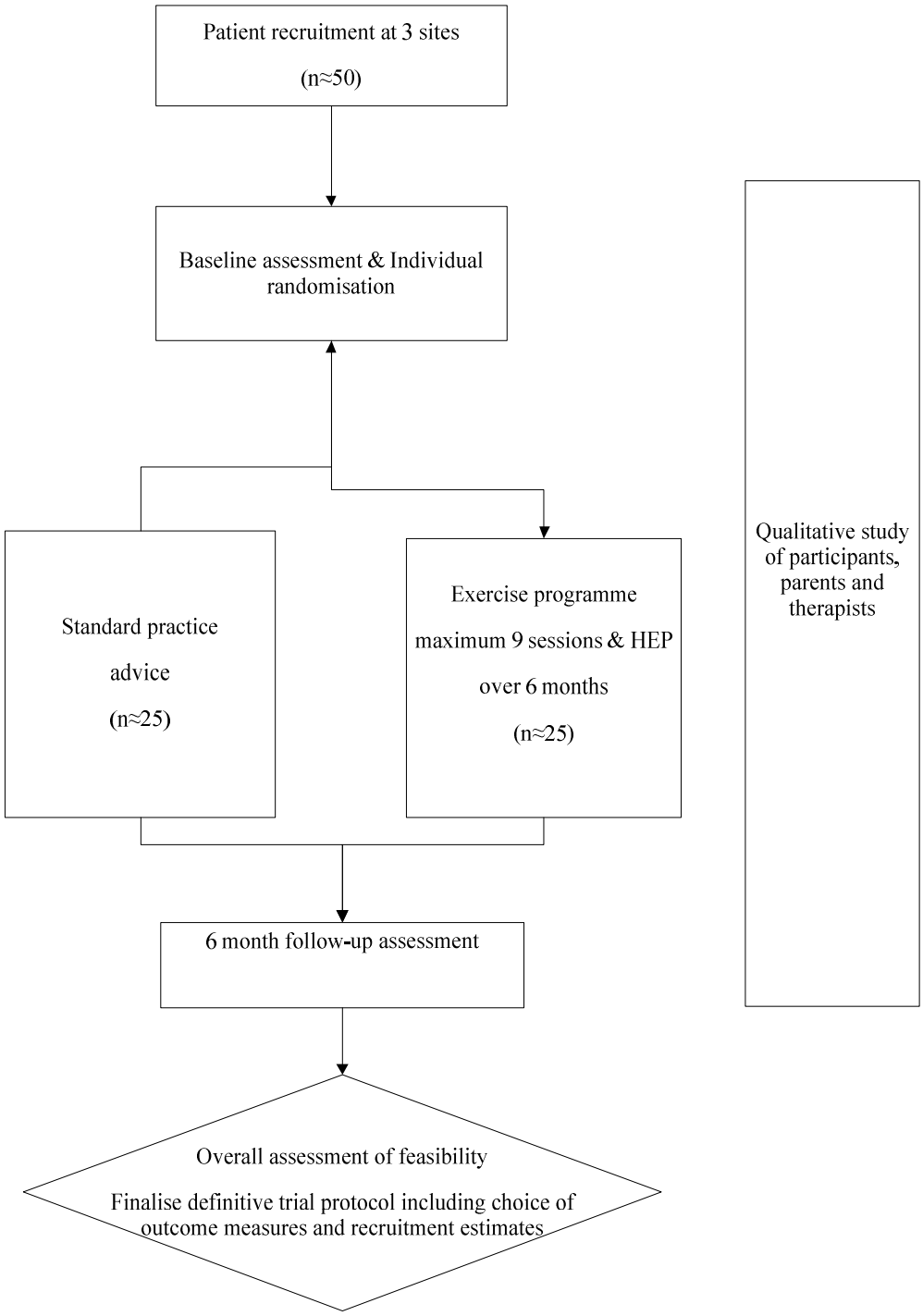
The study will be reported in line with the CONSORT (*Consolidated Standards of Reporting Trials)* statement (Lancet 2001, **357:** 1191-1194).

2 Trial Design

2.1 Summary of the pilot trial

We plan to randomise 50 participants in the pilot RCT to evaluate an exercise intervention compared to usual care (control arm) for patients with mild to moderate AIS. This pilot trial will test recruitment including willingness to be randomised, acceptability of the intervention, ease of delivery within the NHS, data collection and outcome measures. This will allow the evaluation of the viability of a definitive RCT and to finalise a trial protocol. The exercise intervention and control arm have been developed through a systematic literature review, a survey of current practice and consultation with patients and expert clinicians.

2.2 Flow Diagram



2.3 Aims and Objectives

2.3.1 Aims

The aim is to carry out a pilot RCT to:

1) Develop and refine a best evidence intervention, ensuring that it can be delivered within the normal patterns of NHS delivery
2) Assess the key parameters needed to finalise the design and project management plan for a definitive multi-centre RCT to evaluate the clinical and cost-effectiveness of scoliosis-specific exercise treatment in AIS in comparison to standard practice.

2.3.2 Objectives

These aims will be achieved through the following objectives:-

1) To randomise 50 adolescents to the pilot RCT at three participating hospital trusts. The willingness of individuals, their families and surgeons to take part in randomisation needs to be established as this is vital to the success of a future definitive RCT.
2) To finalise a main trial protocol, including the choice of outcome measures. The main issues in outcome measures are the need to reduce as much as possible unnecessary exposure to ionising radiation, and to ensure outcomes are responsive to patients' and clinicians' concerns.
3) To assess and finalise the training requirements for the intervention delivery in the main trial.

2.4 Eligibility for pilot RCT

2.4.1 Inclusion criteria

- 10-16 years olds with Adolescent Idiopathic Scoliosis (AIS).
- Mild to moderate AIS, defined by a Cobb angle of between 10 - 50° (measured radiographically).

2.4.2 Exclusion criteria:

- Individuals who have had previous surgery or are on a waiting list for spinal surgery within the next 6 months.
- Individuals with non-idiopathic scoliosis, for example congenital malformations, syringomyelia, neurofibromatosis, spina bifida, polio and cerebral palsy.

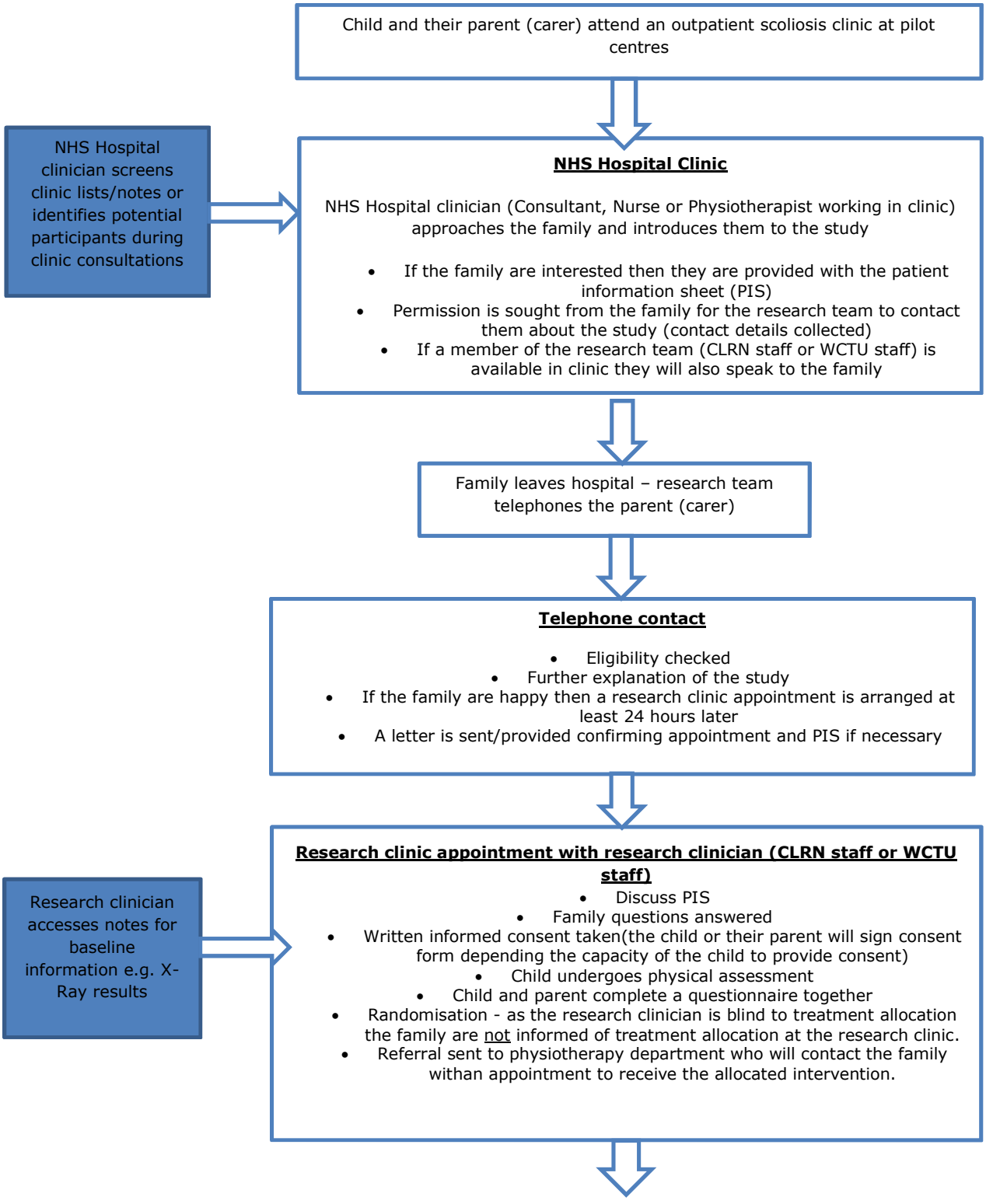
Other treatments including bracing and previous physiotherapy are not exclusion criteria.

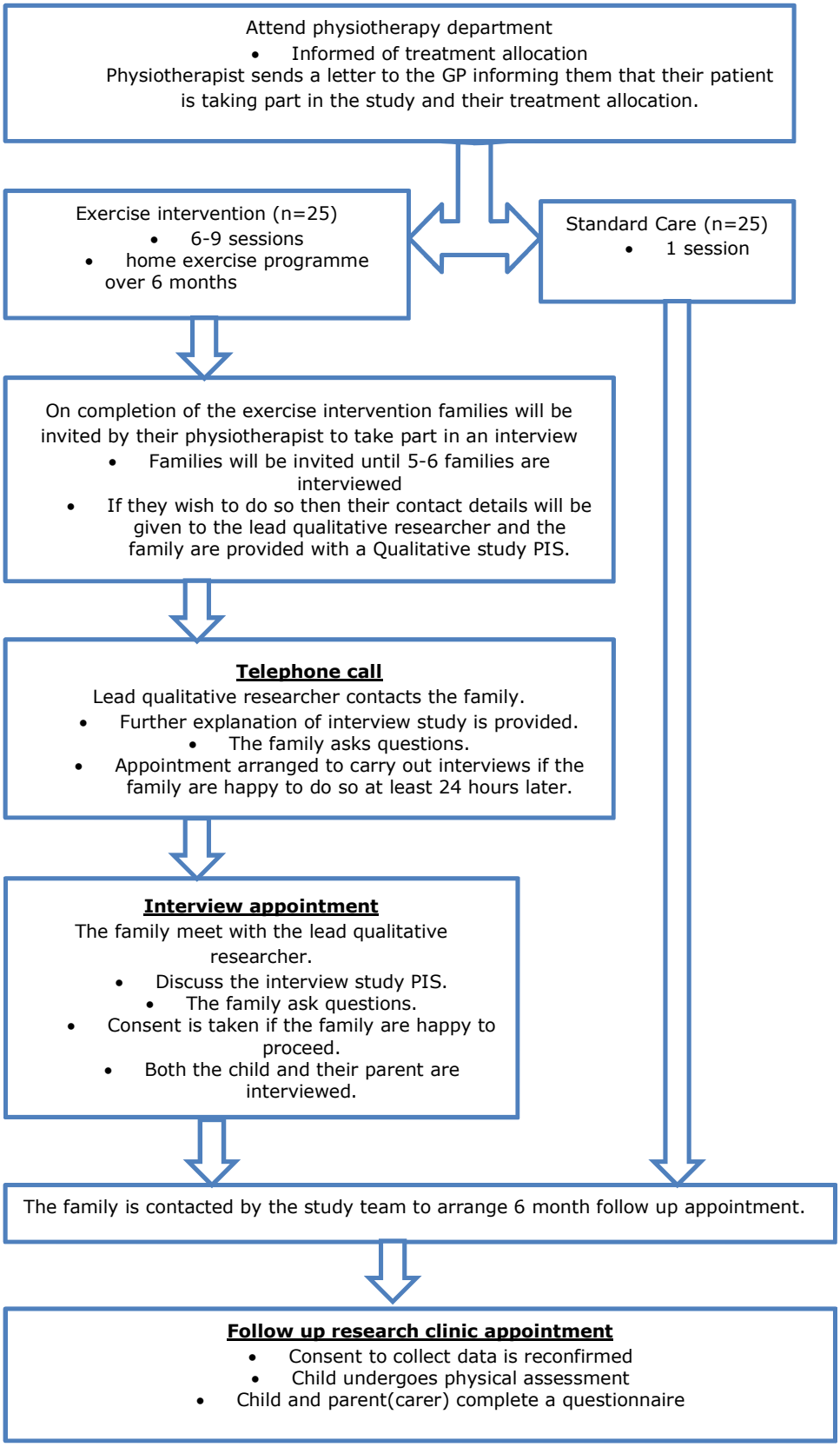
2.5 Informed Consent

We will follow the MRC guidance on seeking consent from children to participate in research (MRC 2004). Where a child is assessed as competent to consent to take part in the study, we will seek his or her consent. In addition, we will seek agreement from parents to allow their children to participate. Where a child is judged not to have capacity to consent to participate, consent will be obtained from his or her parent or guardian and agreement will also be sought from the child. Thus in all cases we will have agreement from both the child and the parent. Researchers responsible for obtaining consent will have training in seeking consent from children and assessing capacity to consent (from Dr Slowther and a Paediatrician with research expertise). We will take care to provide information that is age appropriate and information sheets will be developed with input from a child with the condition and a parent. Participants will be reminded at regular and pertinent intervals that consent is voluntary and can be withdrawn at any stage.

The initial approach will be made by a member of the clinical team responsible for the care of the child (See Figure 2 for flowchart describing a participant journey through the study). A verbal explanation of the study will be provided either by a member of the clinical team, Comprehensive Local Research Network (CLRN) or locally employed research staff, depending on the context of each site. The research team will only be provided with details of those families that have provided verbal consent to be approached and have their details shared. The research team will contact the family and if they are interesting in taking part then a research clinic appointment will be arranged at the same hospital they attended for their scoliosis management. They will have at least 24 hours to consider their involvement before attending for this appointment. The research clinic will be run by a research clinician (either a nurse or physiotherapist employed by Warwick Clinical Trials Unit (WCTU) or the CLRN). At the research clinic appointment, informed consent will be obtained from the child and parent (carer) following discussions and any questions having been answered.

Figure 2 Participant Journey through the study




Attend physiotherapy department
• Informed of treatment allocation
Physiotherapist sends a letter to the GP informing them that their patient is taking part in the study and their treatment allocation.
Exercise intervention (n=25)
• 6-9 sessions
• home exercise programme over 6 months
Standard Care (n=25)
• 1 session
On completion of the exercise intervention families will be invited by their physiotherapist to take part in an interview
• Families will be invited until 5-6 families are interviewed
• If they wish to do so then their contact details will be given to the lead qualitative researcher and the family are provided with a Qualitative study PIS.
Telephone call
Lead qualitative researcher contacts the family.
• Further explanation of interview study is provided.
• The family asks questions.
• Appointment arranged to carry out interviews if the family are happy to do so at least 24 hours later.
Interview appointment
The family meet with the lead qualitative researcher.
• Discuss the interview study PIS.
• The family ask questions.
• Consent is taken if the family are happy to proceed.
• Both the child and their parent are interviewed.
The family is contacted by the study team to arrange 6 month follow up appointment.
Follow up research clinic appointment
• Consent to collect data is reconfirmed
• Child undergoes physical assessment
• Child and parent(carer) complete a questionnaire

2.6 Planned investigations

2.6.1 Evaluation of an exercise intervention compared to usual care

2.6.1.1 Development of the interventions

A period of intervention development has been undertaken. This has included carrying out a survey to establish current usual practice to inform the content of the control arm. A review of the current evidence base was carried out including the updating of the most recent available systematic literature review (Romano et al. 2010). Fifteen clinicians experienced in the management of AIS attended an intervention development day in April 2012. We have utilized their knowledge and experience to refine the intervention, establish training needs and ensure its acceptability to the clinical community. User groups and participants will also be consulted on the suitability of the intervention, outcome measures and trial materials.

2.6.1.2 The exercise intervention

Aims of the exercise intervention

The aims of the exercise intervention are based on the European guidelines for the management of AIS (Negrini et al. 2012, Weiss et al. 2008). Broadly, the aims are to provide a treatment to avoid surgery and or bracing. The specific aims of the exercise intervention are:

1) Achieve active auto-correction of spinal deformity
2) Address restricted range of movement that may prevent active auto-correction
3) Achieve maintenance of the auto-corrected position during movement including integration in activities of daily living
4) Improve sensorimotor integration and balance reactions while maintaining the corrected position
5) Provide education and support for the participant and family
6) Promote strategies to encourage adherence to the exercise programme

Delivery of the exercise intervention

Participants will be asked to carry out the exercise programme primarily as a daily home exercise programme with initial physiotherapy assessment and regular therapy review sessions (up to a maximum of 9 sessions over the 6 months) to provide support, encourage adherence, and allow monitoring and progression of the exercises. Although some clinicians, particularly those following the European schools of thought, advocate prolonged in-patient exercise programmes, recent evidence suggests that such intensive programmes that disrupt normal schooling and socialisation are not necessary (Weiss and Goodall 2009).

Content of the exercise intervention

Each participant will be assessed by their physiotherapist and given an individualised exercise programme based on the presenting spinal deformity. The first step of the exercise programme is to teach the participant to correct their posture (auto-correction to reduce the spinal deformity). Visual, tactile and verbal feedback will facilitate this. Once this has been achieved the participants will be given additional exercises that progressively challenge their ability to maintain the corrected posture by altering position, adding load or resistance, adding movement or distractions and incorporation into activities of daily living.

Physiotherapists will be provided with a manual containing a library of exercises that address the aims of the exercise programme from which they can select the appropriate exercises for each participant. The participant will be given a small number of exercises at any one time which will be replaced by exercises of increasing difficulty as mastery of each exercise is achieved. Participants will carry out up to 30 minutes of exercises each day.

Adherence with the exercise programme will be vital to its success. Many of the approaches in Europe provide extensive supervised sessions. However, this is not feasible for the NHS to provide supervision for the duration and frequency reported in the literature (e.g 5 days a week for 4 weeks (Rigo et al. 2008)). Instead we will utilise behavioural methods and techniques including exercise contracts, an on-line exercise diaries and on-line chat forum moderated by the physiotherapists at each centre to promote adherence (Sheeran, Trafimow and Armitage 2003).

The on-line resources will be designed so that they can be hosted by NHS.net, are compliant with NHS security standards and can be disseminated readily into the NHS. They will provide physiotherapists and participants with a structured approach to prescribing/progressing the physical and behavioural elements of the exercise programme, and a diary for participants to record their progress and concerns (including any adverse events). It will only be accessible to the treating therapist, individual participants (and their parents depending on the age of the child) and research team. Each participant will be provided with a unique user name and password to ensure that all information is confidential and protected. We are confident that all children will have access to computers – the vast majority through home provision (Harris 1999) or school or library alternatives. We will check computer access carefully as the study progresses and will provide alternative materials available if this is difficult and likely to be a barrier. The behavioural strategies,

which are not monetary in nature, have been successful in other areas of health intervention for adolescents. Exercise diaries are effective in improving adherence to home exercise programmes, particularly if the participant is aware that the diary is being monitored by a health professional (Moseley 2006). The diary will form a useful point of discussion in the consultations between participants and physiotherapists. As well as recording number of sessions attended, we will also ask therapists to make an assessment of the participants' adherence.

Alongside the exercise programme and adherence strategies, the physiotherapist will also provide education and support for the participant and family. This will include discussions about the participant's expectations of the exercise programme, education about AIS including participation in sporting activities and address any concerns or worries (e.g. concerns about the exercises, concerns about body image) of the participant and/or parents.

Physiotherapist training

The physiotherapists delivering the exercise intervention will receive between one and two day's training with follow-up support from the research team. From the information collected at the intervention development day, we anticipate that the majority of clinical skills for exercise prescription already exist but some specific training about exercise prescription in patients with AIS will be included. A health psychologist (Dr Coulson) will provide training on the use of the adherence strategies, managing psychosocial issues related to children and the on-line forum. Training in trial procedures will ensure that the physiotherapists have an understanding of the need to comply with the trial protocols and governance procedures. The physiotherapists will also be trained in delivering the control intervention. The interventions will be documented in a manual, along with training materials and a theoretical justification for the various components. Support will be provided by the research team based at WCTU and two physiotherapists who have specialized in AIS and are collaborators on the trial (Anne Richards and Steve Bunce).

2.6.1.3 The control intervention

Participants randomised to the control arm will receive 1-2 sessions (up to one hour) with a physiotherapist which will encompass musculo-skeletal assessment, information and advice regarding their condition and support groups (e.g. SAUK), and, if relevant, information about brace use and care. Participants in both arms will continue to attend for orthopaedic review as per standard practice at their centre. The control intervention will be delivered by the same physiotherapists who deliver the exercise intervention.

2.6.2 Qualitative study

We will also conduct a qualitative study alongside the pilot RCT. Participants, their parents and the physiotherapists delivering the intervention will be interviewed. Our aim is to explore factors that influence the acceptability of the trial and interventions, issues influencing exercise adherence, and appropriateness of the chosen outcome measurement to participants. Further details are provided in a separate protocol.

2.7 Outcome Measures

2.7.1 Criteria for progression to a randomised controlled trial

The primary outcome of this feasibility trial is to assess if the criteria for progression to a full RCT has been achieved. The progression criteria will be:

1. To demonstrate that the assumptions underlying the sample size, in particular the rates of progression are as anticipated in three centres, that variances are within our estimated range, and that we can achieve or better the recruitment target in these three centres.

   We estimate the definitive trial will include between 300-400 participants. This would allow detection of a standardised difference of 0.3, equating to a clinically important 6 degree difference between groups in the Cobb angle (Negrini et al. 2010) (SD of 15 degrees using 80% power, alpha <.05, loss to follow-up of 30%), and also a relative risk reduction of 1.4 in the numbers proceeding to surgery, assuming that 20% of the control group progress to surgery.

2. That we have sufficient numbers of centres, with sufficient numbers of participants in order to finalise the recruitment strategy for a main trial.

   Thirty-five NHS Trusts managing AIS in the UK have been identified that could potentially recruit participants in the main trial. There is a wide range of permutations of time, rate of recruitment and number of centres recruiting that could achieve the anticipated sample size but the optimal strategy needs to be finalised. We will also be able to confirm whether patients and their families are willing to accept randomisation as opposed to sourcing exercises themselves, and whether our estimates of the numbers potentially eligible, meeting the various inclusion and exclusion criteria, and finally being randomised are accurate.

3. To have developed an intervention which, based on theoretical models, has sufficient therapeutic dose to limit or reverse progression of curvature and has maximal chance of engaging adherence in adolescents. We must demonstrate that we can deliver a theoretically sufficient dose within current and reasonable levels of NHS resourcing, and that greater than 60% of adolescents will have attended all

supervised sessions and provide evidence that they are undertaking exercises at home.

2.7.2 Outcome measures

Outcome measures will be evaluated to ensure they are appropriate for use in a large, multi-centre trial and balance respondent burden, cost of data collection and value of the data appropriately. Implications for application of these outcome measures will be assessed through consultation with patients via the qualitative study and research clinicians via informal feedback.

Primary and secondary outcome measurements will be taken at baseline and six months. This will allow time for the interventions to be completed and will allow us to assess the feasibility of data collection and adherence to the exercise interventions.

2.7.2.1 Primary outcome measure

The primary outcome measure for the pilot RCT will be Cobb angles as measured by X-ray at 6 months after randomisation. We anticipate that the primary outcome measures for a main RCT study will be the progression/stabilisation of curvature quantified by the Cobb angle. Traditionally the measurement of Cobb angle required repeat X-ray but many centres have invested in topographical measurement equipment (e.g. ISIS-2 measurement system) that allows for assessment of Cobb angle and rib hump without exposure to X-ray. We will explore whether it will be feasible/cost-effective to use the ISIS-2 measurement system in all centres in the main trial (as it might be the case that equipment has to be purchased for some sites). Although the measurement of outcome is not essential to the assessment of feasibility, we feel it is prudent to capture outcomes as it is likely that the pilot could contribute data to a future definitive trial (and hence reduce the cost). In our proposed time table we will probably not have 6 month outcome for all participants. This data is not needed for the assessment of feasibility. However, we will continue to collect the follow up data after the end of the funded study period, so that the data are available for later publication and/or inclusion in a future definitive trial if appropriate. The data will be made available to the funders.

2.7.2.2 Secondary outcomes

We will also pilot a range of secondary outcomes. There are a range of quality of life measures available for AIS - an expert consensus meeting suggested that aesthetics, quality of life, disability, back pain and psychological well-being were the most important outcomes for conservative treatment of AIS (Negrini et al. 2006). Based on this we will collect the following data:

- Disease specific functional measure: Scoliosis Research Society 22 Questionnaire (Asher et al. 2003)

- Participant perceived spinal deformity: Spinal Appearance Questionnaire (Sanders et al. 2007)
- Generic functional measure: Paediatric Outcomes Data Collection Instrument (Lerman, Sullivan and Haynes 2002)
- Exercise tolerance and respiratory function
- Health related quality of life measures: EQ-5D, Health Utilities Index and SF-12
- Resource use for economic analysis
- Brace wearing status
- Progression to surgery

2.8 Sample size

We will not be able to estimate the effect size for exercise in the pilot trial with any reasonable degree of certainty, but we have sized the pilot trial so that we can estimate the baseline variance in the outcome measures which is one of the most important drivers of any sample size estimate. A minimum of 30 participants are needed to estimate the variance of parameters underlying the sample size estimate (Lancaster, Dodd and Williamson 2004). We have chosen a target of 50 as this allows for better estimation of recruitment rates at each of the three centres. We plan to synthesise data from the systematic review, clinical opinion and the pilot data to derive a target effect size for the main trial.

2.9 Recruitment and randomisation

2.9.1 Identifying potential participants

We plan to run the randomised pilot trial in 3 of the 35 NHS trusts specialising in scoliosis management. Participants will be recruited directly from spinal deformity or scolioisis clinics at the three centres. Patients with AIS will be approached to participate in the feasibility study by clinicians who will be supported by a physiotherapy research fellow and/or CLRN research nurses. We have reviewed attendance rates at each of the feasibility sites and, for the types of participants we seek, expect referral of around 4 eligible participants per month per site. Assuming 40% agree to participate, we will recruit 5 participants per month during the feasibility stage, and require an estimated 10-12 months to achieve the target of 50 participants.

2.9.2 Method of randomisation

Randomisation will be on an individual basis using the WCTU telephone randomisation service. Randomisation will be stratified by centre to control for any local differences and in case mix between sites. For the main study we anticipate stratifying randomisation by bracing regime at study entry and we will evaluate this in the feasibility stage.

2.10 Post-randomisation withdrawals and exclusions

Participants may withdraw from the trial intervention, and/or the whole trial at any time without prejudice. If a participant withdraws from the trial intervention, participants will be followed-up wherever possible and data collected as per protocol until the end of the trial. The only exception to this is where the participant also explicitly withdraws consent for follow-up.

Participants may also be withdrawn from the trial at the discretion of the Chief Investigator, the lead local investigator and/or Independent Monitoring Committee due to safety concerns.

2.11 Blinding of treatment allocation

It will be impossible to blind the therapists involved in delivering the interventions and the participants receiving them. However we will structure the outcome assessment so that outcome assessors are blinded. We will test the integrity of the blinding by asking assessors to guess which allocation participants had at the 6 month follow up point.

2.12 Compliance/contamination

During the pilot RCT, the treating therapists will record the number of physiotherapy sessions attended by each participant and the content of the physiotherapy session on a treatment log. Participants will also complete an online-exercise diary so that compliance with the home exercise programme can be monitored.

We will periodically observe the consent process and baseline and follow-up assessments. Quality control visits will also be carried out to observe physiotherapy sessions. Quality assurance checks will be undertaken by the WCTU to ensure the integrity of randomisation, study entry procedures and data collection.

3 Methods and Assessments

3.1 Schedule of delivery of intervention and data collection

Table 1 Pilot RCT events

Event/information collected	Usual clinic appointment	Baseline assessment & randomisation	Exercise intervention delivered over 6 months (6-9 sessions)	Control intervention 1-2 sessions	Follow up assessment (6 months post randomisation)
Initial screening of participants expressing interest: Inclusion/exclusion criteria	√				
Demographics and past medical history		√			
Cobb angle: X-ray and ISIS-2 measurements	√	√			√
Disease specific functional measure: Scoliosis Research Society 22 Questionnaire		√			√
Generic functional measure: Paediatric Outcome Data Collection Instrument		√			√
Participant perceived spinal deformity: Spinal Appearance Questionnaire		√			√
Quality of life: EQ5D, Health Utilities Index, SF-12		√			√
Brace wearing status		√			√
Intervention delivered			√	√	
Treatment log completed by physiotherapist			√	√	
Online exercise diary completed by participant			√		
Recording of any progression to surgery					√

4 Adverse Event Management

4.1 Definitions

4.1.1 Adverse Events (AE)

An adverse event is defined as any untoward medical occurrence in a subject which does not necessarily have a causal relationship with this treatment.

4.1.2 Serious Adverse Events (SAEs)

An SAE is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition.

4.2 Reporting SAEs during the pilot RCT

In addition to those described above. We will define the following as a serious adverse event:

A significant increase or onset of pain or other symptoms (e.g. neurological symptoms) within 48 hours of attending a physiotherapy session or taking part in an exercise session causing the participant to reduce their normal activities (e.g. absence from school, cutting down on sport) for greater than 3 days.

Due to the nature of AIS and exercise therapy, it is expected that the following may occur during the pilot RCT and, therefore, will not be reported to the MREC. They will be recorded as an AE:

The participant needs surgery due to curve progression.
The participant needs bracing due to curve progression.
Mild muscle soreness normally associated with exercise (lasting up to 48 hours).

All adverse events will be recorded in the Case Report Form (CRF) for participants by local clinical and research staff at assessment for routine return to the research office. Any AEs fitting the criteria for 'serious' as defined above will be recorded on the SAE report form provided and faxed to WCTU (fax number 02476 150549) within 24 hours of the investigator becoming aware of the event. Physiotherapists who deliver the interventions

will be trained in the reporting of AE and SAEs. All SAEs will be recorded in the trial database and reported to the Independent Monitoring Committee.

The study manager will liaise with the clinician to compile all the necessary information. The Trial Co-ordinating Centre is responsible for reporting adverse events to the sponsor and ethics committee within required timelines. The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the Principal Investigator at the site involved and the Chief Investigator and this will be recorded on the SAE form. SAE's which are deemed to be both unexpected and related to the intervention will be reported to the main REC within 15 days of receipt.

4.3 End of the pilot RCT

The pilot trial will end when 50 patients have been recruited and completed their 6 month follow-up. The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Independent Monitoring Committee
- Funding for the trial ceases

The Main Research Ethics Committee (MREC) will be notified in writing if the trial has been concluded or terminated early.

5 Data Management

5.1 Data collection and management

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act, ICH and MRC good clinical practice guidelines. Access to stored information will be restricted to authorised personnel.

Participants will be identified using a unique trial number. Personal identifying information will be held at WCTU. Personal contact details of trial participants will be needed to organise the baseline and follow-up assessments as well as interviews for the qualitative study. This information will be filed separately from all other trial information. We will retain paper records of participant details. Personal information will also be made available to the treating therapist when the participant is referred for the trial treatment (on the physiotherapy referral form as is usual clinical practice).

The CRFs, physiotherapy treatment logs and online exercise diary will be designed by the research fellows in conjunction with the Chief Investigator, Co-investigators and Statistician. The original CRFs will be sent to WCTU with a copy retained in the site file at the hospital where the participant attended. The physiotherapists will return the physiotherapy treatment log to WCTU when the participant has completed treatment. The online exercise diary will be downloaded after the participant has completed follow up.

Data will be entered onto a WCTU database by a member of the trial team. Data will be subject to validity checks and additional data checking procedures to assure quality of data entry as per WCTU SOPs.

5.2 Database

The WCTU Programming Team will be responsible for developing the pilot RCT database used for randomisation, online exercise diaries, discussion forum, CRF data entry and trial management. A third party software component will be used for the forum with all other software being developed by the WCTU Programming Team. All development work will be completed in accordance to the WCTU's Software Development standard operating procedure (SOP-14).

The ACTIVATES system will use a SQL Server 2005 enterprise edition database and an ASP.NET web application running on IIS6. The web server, SQL server and backup devices are all hosted in a purposed built data centre managed by the University of Warwick's Applications and Hosting Service Team.

The online exercise diary and discussion forum will be accessed by participants and therapists whom have been allocated a user name and password. Access to randomisation, CRF data entry and trial management components will be restricted to members of the ACTIVATES trial team based within the WCTU building.

5.3 Archiving of Trial Data

Data will be securely stored by the WCTU for 5 years after completion of the trial.

6 Statistical Analysis

6.1 Assessment of progression to a randomised controlled trial

Pilot RCT data will be summarised and reported in accordance with CONSORT guidelines for randomised controlled trials (Schulz et al. 2010). We will report the number of participants approached, the numbers meeting the eligibility criteria, agreeing to randomisation, numbers attending the trial treatment sessions, the overall proportion of people who attend 60% of the sessions and use of the online exercise diary. We will report the parameters needed for sample size estimation, and descriptors of the recruited cohort. Completion of

measures will also be recorded alongside descriptive data. In addition at each site we will also review attendances over the last 2 years to determine the proportions that are likely to progress to surgery as this will be considered in the final calculation of the sample size.

By the end of the study we will be able to determine how many centres we require, how many participants they should be able to recruit, and how long we require them to recruit to the trial for, as well as the variances needed to inform the final sample size calculations. We will have an intervention that is manualised and ready for dissemination in a definitive trial. The overall assessment of feasibility will integrate all of the components of the evaluation. We will specify a protocol for a future trial in accordance with the commissioning brief.

6.2 Economic analysis

The feasibility of conducting an economic evaluation of the exercise intervention will be assessed during the course of this study. This will involve consideration of the practicalities and difficulties associated with an assessment of the costs to providers, individuals and, more broadly, to society entailed by the introduction of the exercise intervention. As part of the pilot study, we will evaluate the performance of alternative client service receipt inventories in collecting resource utilisation data. The pilot study will also involve an identification of the appropriate sources of unit cost data for potential resource consequences and an assessment of how much primary costing research will be required. An assessment will be made of the best possible way of expressing the cost-effectiveness of the exercise intervention. Outcome measures such as progression/stabilisation of curvature preclude cost-effectiveness comparisons with health interventions more broadly. Moreover, they overlook the potential consequences of the exercise intervention on broader aspects of health-related quality of life and individuals' preferences for those broader consequences. We will therefore review and pilot a number of multi-attribute utility measures in the pilot study including the EuroQol EQ-5D, SF-12 and the Health Utilities Index, with the view to estimating quality-adjusted life years (QALYs) in the subsequent trial-based economic evaluation.

7 Trial Organisation and Oversight

7.1 Ethical conduct of the trial

7.1.1 Ethical arrangements

Ethical and governance approval will be sought from MREC and local hospital R&D departments via the Integrated Research Application System prior to study commencement. There are additional ethical issues when involving young people in research and therefore

we will follow the MRC guidance on medical research involving children (MRC 2004). The consent process has been outlined previously in this document.

Confidentiality will be maintained at all times except when the information disclosed relates to a child "at risk". Researchers and clinicians working on the study have a legal obligation to pass on information if they feel a child is 'at risk'.

'Where a child or young person divulges that they or others are at risk of significant harm, or where the researcher observes or receives evidence of incidents likely to cause serious harm, the researcher has a duty to take steps to protect the child or other children' (National Children's Bureau 2003).

All researchers working on the study will be trained in child protection issues and will have a cleared enhanced Criminal Records Bureau check. Training will be provided by a specialist in medical ethics (Dr Anne Slower) and a paediatrician with research experience. Any concerns about a child will be reported immediately to the Chief Investigator and the lead local investigator who will take the appropriate steps to protect the child involved. We will highlight the limits to confidentiality to the child and their parent as part of the consent process and will be included in the information sheets and consent forms.

To ensure confidentially, all study documentation will identify participants by a unique study number, and will otherwise be anonymised. Recordings, transcripts and other data capture forms will be kept in a locked filing cabinet in a locked office in compliance with the Data Protection Act (1998) and the Standard Operating Procedures of the WCTU.

7.1.2 Risks and benefits

The risks to the participants are small. There is no evidence available to suggest that either the control or experimental interventions are harmful, whilst the small amount of evidence suggests that exercise may help with the effects of mild/primary AIS. There is the possibility of participants experiencing temporary discomfort as a result of the exercises.

7.1.3 Informing potential participants of risks and benefits

The patient information leaflets will provide potential participants and parents with information about the possible risks and benefits of taking part in the trial. They will be given the opportunity to discuss the trial with the research nurse/therapist. We will inform participants, their parents and consultants if new information comes to light that could affect their willingness to participate in the research.

7.2 Sponsor

The trial will be sponsored by the University of Warwick, who will be responsible for ensuring that all aspects of research governance are put in place before activation of sites. The conduct of the trial will be monitored by the trial management group who will be responsible for the day-to-day running of the trial. The trial will be conducted in accordance with the Standard Operating Procedures of WCTU.

7.3 Indemnity

Staff employed by the NHS will be covered by the Clinical Negligence Scheme for NHS Trusts. Staff employed by the University of Warwick will be covered by the University's clinical trial insurance. Negligent harm cover will be provided by standard NHS arrangements (HSGG(96)48). NHS Indemnity does not give indemnity for compensation in the event of non−negligent harm, so no specific arrangements exist for non−negligent harm for this trial.

7.4 Trial timetable and milestones

This pilot RCT is part of a 2 year feasibility study including a 6 month intervention development phase (Table 2). Recruitment to the pilot study will begin following this developmental phase. We aim to complete the pilot study within an 18 month period (recruiting for 12 months) so that all participants can be followed up within the duration of the feasibility study although not all data may be available for inclusion in the final report (See Section 3.7.2.1). Data analysis, report writing and the full trial protocol will be undertaken from month 20 onwards.

Table 2 Project timetable

Year	1						2					
Month	2	4	6	8	10	12	14	16	18	20	22	24
Intervention development phase												
Governance approvals												
Recruitment (n≈50)												
Follow-up (6 months post randomisation)												
Analysis, write-up and production of main trial outline protocol												

7.5 Trial administration

The trial will be coordinated at WCTU. Dr Mark Williams will be responsible for the day to day running of the trial. He will be assisted by other research fellows based at the WCTU (Peter Heine and Dr Esther Williamson) to update the systematic review, carry out the clinician survey, develop the intervention, liaise with user groups and expert clinicians, train the physiotherapists to deliver the intervention, train research staff to consent, randomise and assess participants, and carry out quality assurance activities.

7.6 Trial Management Group (TMG)

The Trial Management Group, consisting of the Chief Investigator, the research fellows involved in the day-to-day running of the study, the trial statistician and health economist will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the co-investigators or independent monitoring committee as necessary. Additionally all co-investigators will meet on a 3 monthly basis.

7.7 Independent monitoring committee

As this is a feasibility study a Trial Steering Committee and Data Monitoring and Ethics Committee will not be appointed. Instead, an Independent Monitoring Committee will be appointed to primarily review serious adverse events.

7.8 Trial Registration

This trial is registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register: ISRCTN90480705

7.9 Essential Documentation

A Trial Master file will be held securely at the coordinating centre, in accordance with WCTU SOPs. Investigator Site Files will be held at each participating centre.

8 Monitoring and quality assurance of trial procedures

The trial will be conducted in accordance with the Standard Operating Procedures of WCTU. The sponsor will ensure that investigator(s)/institutions will permit trial-related monitoring, audits, REC review and regulatory inspections, providing direct access to source data/documents.

Regular monitoring visits to trial centres will be carried out. Compliance with the trial protocol and GCP will be monitored by observing assessment, consenting and randomisation of trial participants by research staff and observing physiotherapy sessions. CRFs will be routinely checked for missing data or errors and issues addressed as they arise. Trial records (i.e. online exercise diaries or physiotherapy treatment logs) will be scrutinised to identify potential problems with adherence to the intervention.

Single data entry will be carried out with a subset of forms being double entered (10%) to check for accuracy.

9 Dissemination and Publication

We expect to prepare a HTA monograph of the project in accordance with usual HTA practice. In addition to providing an overall assessment of feasibility for a definitive trial, there will be a number of other important outputs. These will include an intervention manual and behavioural support package and papers to include an updated systematic review, clinician survey, assessment of the ISIS-2 system, publication of pilot randomised data and study protocol, and important new qualitative information to guide practice and development in scoliosis management.

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PROTOCOL

ACtive Treatment for Idiopathic AdolescenT Scoliosis (ACTIvATeS): Qualitative study

Version 1.0 (2/7/2012)

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Protocol Amendments:

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Names and contact numbers of ACTIvATeS study team:

Study Lead
Dr Mark Williams
Research Fellow
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
02476574648
Email: m.a.williams.3@warwick.ac.uk

Sponsor
Dr Peter Hedges
Director of Research Support Services
The University of Warwick
Kirby Corner Road
Coventry CV4 8UW
Tel: 024 7652 3859
Email: P.A.Hedges@warwick.ac.uk

Chief Investigator
Professor Sallie Lamb
Director
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
Tel: 024 7657 4658
Email: s.lamb@warwick.ac.uk

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National Institute of Health Research
Health Technology Assessment (HTA)
Agency

http://www.hta.ac.uk/

Co-applicants
Dr Karen Barker
Director of Therapy Research
Nuffield Department of Orthopaedics
Rheumatology and Musculoskeletal
Nuffield Orthopaedic Centre NHS Trust
Windmill Road
Oxford OX3 7LD
Tel: 01865 738080
Email: Karen.Barker@noc.nhs.uk

Professor Jeremy Fairbank
Consultant Spinal, Orthopaedic and Trauma Surgeon
Nuffield Department of Orthopaedics
Rheumatology and Musculoskeletal
Nuffield Orthopaedic Centre NHS Trust
Windmill Road
Oxford OX3 7LD
Tel: 01865227374
Email: jeremy.fairbank@ndorms.ox.ac.uk

Mr Ian Harding
Consultant Orthopaedic Surgeon
Frenchay Hospital
North Bristol NHS Trust
Frenchay Park Road
Bristol BS16 1LE
Telephone: 0117 340 3744
Email: Ian.Harding@nbt.nhs.uk

Dr Anne-Marie Slowther
Associate Professor Clinical Ethics
Warwick Medical School
The University of Warwick
Gibbet Hill Road,
Coventry CV4 7AL
Tel: 02476 574513
Email: annemarie.slowther@warwick.ac.uk

Dr Mark Williams
Research Fellow
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
02476574648
Email: m.a.williams.3@warwick.ac.uk

Mr Peter Heine
Research Fellow
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road,
Coventry CV4 7AL
Tel: 02476150989
Email: p.heine@warwick.ac.uk

Dr Francine Toye
Research Physiotherapist
Physiotherapy Research Unit
Nuffield Orthopaedic Centre NHS Trust
Windmill Road
Oxford OX3 7LD
Tel: 01865 737526
Email: Francine.Toye@ouh.nhs.uk

Dr Esther Williamson
Research Fellow
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
Tel: 02476151665
Email: e.m.williamson@warwick.ac.uk

Dr Ranjit Lall
Trial statistician
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
Tel: 02476 574649
Email: r.lall@warwick.ac.uk

Prof Stavros Petrou
Health Economist
Clinical Trials Unit
Warwick Medical School
The University of Warwick
Gibbet Hill Road
Coventry CV4 7AL
Tel: 02476 151124
Email: s.petrou@warwick.ac.uk

Dr Neil Coulson
Associate Professor in Health Psychology
Faculty of Medicine and Health Sciences
Level B, International House
Jubilee Campus
Nottingham NG8 1B
Tel: 0115 846 6642
Email: neil.coulson@nottingham.ac.uk

Specialist collaborators

Steve Bunce
Clinical Specialist Physiotherapist
Frenchay Hospital
North Bristol NHS Trust
Frenchay Park Road
Bristol BS16 1LE

Anne Richards
Clinical Specialist Physiotherapist
Nuffield Orthopaedic Centre NHS Trust
Windmill Road
Oxford OX3 7LD

Mr Adrian Gardner
Orthopaedic surgeon
Royal Orthopaedic Hospital
Bristol Road South
Birmingham B31 2AP

Independent monitoring committee

Chair:
Sally Kerry
Research Design Service London - Research Adviser
Reader in Medical Statistics
Centre for Primary Care and Public Health
Blizard Institute
Barts and The London School of Medicine and Dentistry
Yvonne Carter Building
58 Turner Street
London E1 2AB
Tel : 020 7882 7208
Email: s.m.kerry@qmul.ac.uk

Mr Jayesh Trivedi
Consultant Orthopaedic Surgeon
Head of the Department of Spinal Studies
Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust
Oswestry SY10 7AG
Tel:01691404088
Email: Glenys.Hope@rjah.nhs.uk (secretary)

Dr Stephanie Clark (Chair of SAUK) supported by Sarah Wiles (Communications Manager) and Laura Counsell (General Manager)
The Scoliosis Association (UK)
Unit 4 Ivebury Court
325 Latimer Road
London W10 6RA
Tel: 0208 964 5343
Email: sarah.wiles@sauk.org.uk
laura.counsell@sauk.org.uk

Dr Alison Rushton
Senior Lecturer in Physiotherapy
School of Health and Population Sciences
College of Medical and Dental Sciences
52 Pritchatts Road
University of Birmingham
Edgbaston
Birmingham B15 2TT
Tel: 0121 415 8597
Email: a.b.rushton@bham.ac.uk

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List of Abbreviations

AIS Adolescent Idiopathic Scoliosis

FT Francine Toye

HTA Health Technology Assessment

ID Identification

IPA Interpretive Phenomenological Analysis

ISRCTN International Standard Randomised Controlled Trial Number

MRC Medical Research Council

MREC Multicentre Research and Ethics Committee

NHS National Health Service

R&D Research & Development

REC Research Ethics Committee

RCT Randomised controlled trial

TMG Trial management group

WCTU Warwick Clinical Trials Unit

1 Background

1.1 Rationale for the qualitative study

Understanding why patients and their family make the decisions they do about their health care can help us to provide the appropriate treatments. Although parents are often used in research to elicit the young person's experience, we believe that we need to seek information directly from the young people in order to determine the feasibility of the proposed intervention (Mahon et al. 1996). An adult may not give such a useful account of the young person's experience (Beresford 1997).

This will be the first qualitative study to explore the experience of young people with adolescent idiopathic scoliosis (AIS) undergoing an exercise programme. Using search filters (see Appendix 1) specifically developed for qualitative research (Centre for Research and Dissemination) we have identified four qualitative studies of AIS and these focused on experiences of scoliosis surgery and bracing (Bull and Grogan 2010, Macculloch et al. 2009, Macculloch et al. 2010, Sapountzi-Krepia et al. 2006)

1.2 Good Clinical Practice

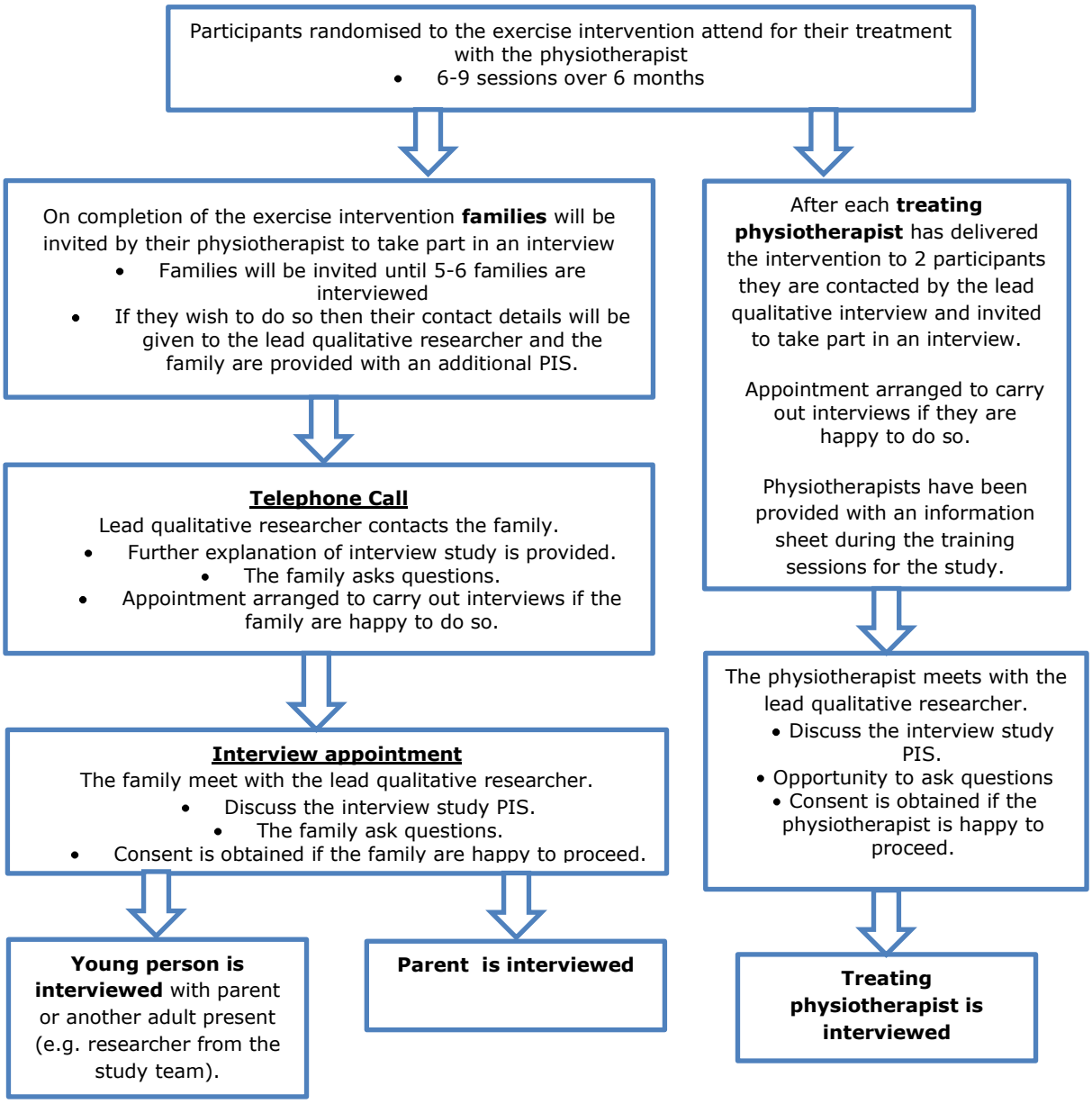
The study will be conducted in full conformance of the principles of the "Declaration of Helsinki" (1964) (as amended in Tokyo, Venice, Hong Kong, South Africa and Scotland), the Medical Research Council (MRC) Good Clinical Practice Guidelines, and applicable UK legislation.

2 Study Design

2.1 Summary of the embedded qualitative study

This qualitative study is embedded in the pilot RCT evaluating the use of exercises in the management of AIS. Specifically, this qualitative study will explore the experiences of a purposive sample of the pilot RCT participants, their parents and physiotherapists delivering the treatments through in-depth semi-structured interviews. The study will use the methods of Interpretive Phenomenological Analysis (IPA)(Smith, Flowers and Larkin 2009).

2.2 Flow Diagram for qualitative study



2.3 Aims

The aim of the qualitative study is to explore factors that influence the acceptability and perception of the trial and interventions, issues influencing exercise adherence, and appropriateness of the chosen outcome measurement to participants.

2.4 Eligibility for the qualitative study

2.4.1 Selection criteria

The individuals eligible to take part in the qualitative study are:

- Young people randomised to the exercise intervention arm of the pilot RCT (10-16 years olds with mild to moderate AIS (Cobb angle of between 10 - 50°) AND their parents (carers)

- Physiotherapists delivering the exercise intervention during the pilot RCT

2.5 Informed Consent

2.5.1 Young people and parents

At initial recruitment to the pilot RCT, young people and their parents will have been asked for consent for the research team to contact them regarding the qualitative study. As part of the on-going process of obtaining consent, at the last treatment session the treating physiotherapist will ascertain if the family are still happy to be contacted by the lead qualitative researcher (Dr Francine Toye) about taking part in an interview. If so, then they will be provided with an information sheet and their contact details will be passed onto the qualitative research team. The treating physiotherapist will not obtain consent for the qualitative study from the participants. Participants will be given at least 48 hours to read the information sheet, and have the opportunity to contact Dr Toye with any further questions. Dr Toye or one of her team will then contact the parent to establish if the family wish to participate and, if appropriate, arrange a suitable time and venue to meet with the family for interview. At this meeting, Dr Toye will discuss the interviews further and answer any questions. She will then be responsible for obtaining consent from the young person and their parent if they agree to take part in an interview. Consent will be obtained separately for each interview – young person interview and parent interview.

We will follow the MRC guidance on seeking consent from young people to participate in research (MRC 2004). Where a young person is assessed as competent to consent to take part in the study, we will seek his or her consent. In addition, we will seek agreement from

parents to allow their young people to participate. Where a young person is judged not to have capacity to consent to participate, consent will be obtained from his or her parent and agreement will also be sought from the young person. Thus in all cases we will have agreement from both the young person and the parent. Researchers responsible for obtaining consent will have training in seeking consent from young people and assessing capacity to consent (from Dr Slowther and a Paediatrician with research expertise). We will take care to provide information that is age appropriate and information sheets will be developed with input from a young person with the condition and a parent. Participants will be reminded at regular and pertinent intervals that consent is voluntary and can be withdrawn at any stage.

2.5.2 Physiotherapists

Physiotherapists administering the ACTIvATeS exercise intervention will be interviewed on a single occasion after they have delivered the intervention to at least two trial participants. Physiotherapists will be given the information sheet by the study team at the trial onset. They will be given time to read the information sheet in their own time, and have the opportunity to contact the lead qualitative researcher (FT) directly if they have any further questions. When they have had sufficient time to consider their inclusion in the trial, Dr Toye will contact the physiotherapist to establish if they wish to participate and, if appropriate, arrange a suitable time and venue for the interview.

2.6 Planned investigations

All participants (young people, parents and physiotherapists) will have the choice to be interviewed at the hospital or in their own home. Each participant will take part in a single interview with an experienced qualitative researcher (FT). Although we will use an interview schedule, which we have developed with the input of users (young people, parents, health care professionals) and the ACTIvATeS research team, the interviews will be semi-structured in nature, allowing the flexibility to follow leads opened by participants. This is a useful approach in research where the aim is to explore personal meanings (Fontana and Frey 2000, Smith 1995). With written consent, each interview will be digitally recorded and transcribed. Each transcript will be loaded onto software developed for qualitative analysis (Nvivo version 9).

2.7 Sample size

There are not a specific number of participants recommended for a qualitative research study. Qualitative research uses non-probability sampling of small groups of people to gain an 'insight into a particular experience' (Smith et al., 2009). Interpretive Phenomenological Analysis specifically recommends in-depth interviews with small homogenous groups of participants. Experience shows us that between 5-6 in each group (young people and parents) will be sufficient to develop useful themes in order to explore the research aims. We hope to interview all the physiotherapists delivering the intervention dependent on whether they wish to participate in the interview study. It is anticipated that four physiotherapists will be taking part in the pilot RCT.

2.8 Recruitment and randomisation

2.8.1 Identifying potential participants

We plan to run the pilot RCT in 3 of the 35 NHS trusts specialising in scoliosis management, thus young people, their parents and physiotherapists will be identified from these 3 trusts. Young people randomised to the exercise intervention will be identified by the treating physiotherapists at the end of their physiotherapy treatment and the lead qualitative researcher (FT) will be provided with their contact details. The parents of these young people will also be invited for interview. See Flowchart for more details.

3 Adverse Event Management

Adverse events will be managed as described in the protocol for the pilot RCT.

4 Data Management

4.1 Data collection and management

Recordings, transcripts and other data capture forms will be kept in a locked filing cabinet in a locked office in compliance with the Data Protection Act (1998) and the Standard Operating Procedures of the Warwick Clinical Trials Unit (WCTU).

4.2 Archiving of Trial Data

Data will be securely stored by the WCTU for 5 years after completion of the trial.

5 Analysis

Analysis of qualitative data for IPA involves coding the narrative data, and then grouping codes that are conceptually similar together under categories [43]. We will use NVivo (QSR, 2000), a computerised programme for analysing qualitative data, to assist analysis. The analysis will be undertaken by the lead qualitative researcher (FT). To add breadth to the development of thematic analysis, the research team will receive NVivo coding reports at team meetings and be able to comment on coding and interpretation. This will also mean that we have timely feedback on the intervention as we are going through the process of developing it. Interviewees will be invited to check their transcripts for accuracy. We will appoint a patient representative to the Trial Steering Group, and this individual will be asked to comment on the coding. They will not see participant's interview transcripts.

6 Trial Organisation and Oversight

6.1 Ethical conduct of the trial

6.1.1 Ethical arrangements

Ethical and governance approval will be sought from MREC and local hospital R&D departments via the Integrated Research Application System prior to study commencement. There are additional ethical issues when involving young people in research and therefore we will follow the MRC guidance on medical research involving young people (MRC 2004).

6.1.2 Participant confidentiality

Participants will not be named on their interview transcripts. The participants will be identified only by initials and a participants ID number on the Nvivo database. Care will be taken to remove any identifying information given in interviews.

However, complete confidentiality cannot be guaranteed because researchers have a legal obligation to pass on information if they feel a young person is at risk.

'Where a Young person or young person divulges that they or others are at risk of significant harm, or where the researcher observes or receives evidence of incidents likely to cause serious harm, the researcher has a duty to take steps to protect the child or other children' (National Children's Bureau 2003).

All researchers working on the study will be trained in child protection issues and will have a cleared enhanced Criminal Records Bureau check. Training will be provided by a specialist in medical ethics (Dr Anne Slower) and a paediatrician with research experience. Any concerns about a young person will be reported immediately to the Chief Investigator and the lead local investigator who will take the appropriate steps to protect the Young person involved. We will highlight the limits to confidentiality to the young person and their parent as part of the consent process and will be included in the information sheets and consent forms.

6.1.3 Other Ethical considerations

There are ethical issues when involving young people in research. In particular, interviews may be difficult for some young people, and we feel that a supportive adult should accompany each young person in all cases. However, a young person may not talk freely about issues regarding their diagnosis and adherence to exercise with their parent present. Therefore, if both the young person and parent agree, a trained supportive adult (from the study team e.g. a research physiotherapist not involved in the recruitment or assessment of that individual) will be present during the interview. Whilst we recognise that it may be difficult for young people to talk freely about issues regarding their diagnosis and adherence to exercise with their parents present, we must also balance this by recognising that parents (and young people) may be anxious in this situation. If either the young person or the parent asks that the parent be present, then this request will be honoured. The interviewer will encourage the parent to allow the young person to talk freely during the interview. The interviewer will assess whether the presence of a parent has had undue influence in the interview process and record this in the research notes. The health professional in attendance at the interviews, and the researcher (FT) conducting the interviews will have experience of supporting study participants who may become distressed during interviews and will be able to provide information to support the needs of the individual young person regarding their diagnosis and treatment.

6.2 Sponsor

The study will be sponsored by the University of Warwick, who will be responsible for ensuring that all aspects of research governance are put in place before activation of sites. The conduct of the study will be monitored by the trial management group who will be responsible for the day-to-day running of the trial. The study will be conducted in accordance with the Standard Operating Procedures of WCTU.

6.3 Indemnity

Staff employed by the NHS will be covered by the Clinical Negligence Scheme for NHS Trusts. Staff employed by the University of Warwick will be covered by the University's trial insurance. Negligent harm cover will be provided by standard NHS arrangements (HSGG(96)48). NHS Indemnity does not give indemnity for compensation in the event of non−negligent harm, so no specific arrangements exist for non−negligent harm for this trial.

6.4 Qualitative study timetable and milestones

Young people and their parent will be interviewed on the completion of the exercise intervention. Therefore, recruitment of young people and their parents (carers) will be commenced approximately 6 months after the start of recruitment to the ACTIvATeS pilot RCT and will continue until we have recruited the purposive sample we require (estimated to be February 2013 until September 2013).

Recruitment of physiotherapists will be commenced once physiotherapists have delivered treatments to at least two participants (estimated to be December 2012 until March 2013).

6.5 Qualitative study administration

The qualitative study will be led by Dr Francine Toye, based at the Nuffield Orthopaedic Centre in Oxford. Dr Toye will be supported by the main study co-ordination team based at WCTU (Dr Mark Williams, Peter Heine and Dr Esther Williamson).

6.6 Trial Management Group (TMG)

The Trial Management Group, consisting of the Chief Investigator, the research fellows involved in the day-to-day running of the study, the trial statistician and health economist will meet regularly throughout the project. The qualitative study group will meet as part of this. Significant issues arising from management meetings will be referred to the co-investigators or independent monitoring committee as necessary. Additionally all co-investigators will meet on a 3 monthly basis.

6.7 Independent monitoring committee

As this is a feasibility study a Trial Steering Committee and Data Monitoring and Ethics Committee will not be appointed. Instead, an Independent Monitoring Committee will be appointed to primarily review serious adverse events.

7 Monitoring and quality assurance of trial procedures

The trial will be conducted in accordance with the Standard Operating Procedures of WCTU. The sponsor will that ensure investigator(s)/institutions will permit trial-related monitoring, audits, REC review and regulatory inspections, providing direct access to source data/documents.

8 Dissemination and Publication

We expect to prepare an HTA monograph of the project in accordance with usual HTA practice. In addition to providing an overall assessment of feasibility for a definitive trial, new qualitative information to guide practice and development in scoliosis management will be generated and published in peer-reviewed journals.

9 Financial support

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Appendix 1: Qualitative Search Filters

MEDLINE: Search filters for qualitative research AND scoliosis AND under 18
qualitative OR ethno$ OR emic OR etic OR phenomenolog$
hermeneutic$ OR heidegger$ OR husserl$ OR colaizzi$ OR giorgi$ OR glaser OR strauss
van AND kaam$ OR van AND manen OR constant AND compar$
focus AND group$ OR grounded AND theory OR narrative AND analysis OR lived AND experience$ OR life
theoretical AND sampl$ OR purposive AND sampl$ OR ricoeur OR spiegelberg$ OR merleau
field AND note$ OR field AND record$ OR fieldnote$ OR field AND stud
participant$ adj3 observ$
unstructured AND categor$ OR structured AND categor$
maximum AND variation OR snowball
metasynthes$ OR meta-synthes$ OR metasummar$ OR meta-summar$ OR metastud$ OR meta-stud$
“action research"
audiorecord$ OR taperecord$ OR videorecord$ OR videotap$