The MAGENTA protocol: The feasibility and acceptability of conducting a trial investigating the effectiveness and cost effectiveness of graded exercise therapy compared to activity management for paediatric CFS/ME: A feasibility randomised controlled trial

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BACKGROUND

Chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) in children is relatively common affecting between 0.1-2% of secondary school children[1-4]. CFS/ME is defined as "generalised fatigue, causing disruption of daily life, persisting after routine tests and investigations have failed to identify an obvious underlying 'cause'[5, 6]. National Institute of Health & Clinical Excellence (NICE) guidelines recommend a minimum 3 months duration of fatigue before making a diagnosis in children[5].

NICE recommends that children and adolescents with CFS/ME are offered either Cognitive Behavioural Therapy (CBT), Graded Exercise Therapy (GET) or Activity Management[5]. GET stabilises physical activity levels, before gradually increasing at a manageable rate. Activity Management establishes a baseline for all activity (mainly cognitive, such as school and homework, in children and adolescents) which is then increased[5 7]. There is good evidence for the effectiveness of CBT in children with CFS/ME [8-10], however there is little evidence for the effectiveness of GET in children and adolescents although GET is moderately effective in adults [11]. There is also limited evidence of the acceptability of GET for children and adolescents with CFS/ME or on the best method for delivering these interventions in terms of intensity (frequency of sessions) and length of intervention (number of sessions and length of time for follow up).

In addition to estimating study parameters such as the willingness of participants to be randomised and the number of eligible patients[8], feasibility studies can be used to improve recruitment and retention by audio-recording recruitment consultations, evaluating information exchange, and re-training recruiters[9-11]. Integrated qualitative methodology can also be used to investigate participants' view of interventions and study methodology providing an opportunity to improve them prior to the full trial.

In this study we will determine whether it is acceptable and feasible to deliver GET compared with active management as part of a multicentre randomised controlled trial. Integrated qualitative methods will be used to optimise recruitment, retention, the delivery of the intervention and investigate the best method for measuring outcomes.

If MAGENTA is shown to be feasible, the study will continue as a full trial. We anticipate that we will be able to use the data obtained in the feasibility phase for the full trial and plan to recruit participants for a further 18 months with an additional 15 months follow up.

Aims and objectives:

The overall aim of this study is to investigate the feasibility and acceptability of conducting a Randomised Controlled Trial (RCT) to investigate the effectiveness and cost-effectiveness of Graded Exercise Therapy compared to Activity Management for the treatment of CFS/ME in children and adolescents. The specific objectives will inform the design of a full-scale, adequately powered trial which will follow the feasibility study.

The specific objectives are:

1. Assess the number of eligible children and adolescents, the number of children and adolescents, approached, the number recruited and the number retained in the first 6 months of the study.
2. Identify barriers and facilitators to trial recruitment with a view to addressing barriers where possible.
3. Explore issues of retention and understand why people drop out of the study.
4. Assess the acceptability (satisfaction and adherence) of GET and Activity Management.
5. Assess the feasibility and acceptability of using accelerometers to measure physical activity in children and adolescents with CFS/ME.
6. Evaluate whether the two interventions are distinct and being delivered in a consistent manner across centres.

METHOD

Recruitment:

Paediatricians and GPs refer children and adolescents with probable CFS/ME to the Bath and Newcastle specialist CFS/ME services. Eligible children and adolescents and their families will be identified by the clinician conducting the initial assessment in the CFS/ME specialist service. The clinician will briefly describe the study and give interested families a study pack which contains: age appropriate patient information sheets for the young person and their parents as well as the relevant consent or assent forms. The clinician will provide information about the study and obtain written assent/consent for a member of the research team to talk to the young person and parent/carers about the study and for this discussion to be recorded.

The recruiting researcher will be based in the hospital and potential participants can either meet with the recruiter in the hospital on the day of the initial assessment (if the recruiter is available and the family have time), discuss the study on the phone, meet face to face at clinic or meet over skype within 7 days of the initial assessment. At the start of the recruitment discussion (face to face, phone call or via skype), the recruiter will confirm consent/assent for the discussion and check that the parent/young person continues to be happy to have the discussion recorded. Once the recording has started, the recruiter will confirm that consent/assent has been given for the discussion to be recorded before discussing the MAGENTA trial, the study design, interventions, participant burden, potential risks and benefits of taking part.

Young people and parents/carers who wish to take part in the study can either sign the written study consent/assent forms when they meet the recruiter or post the form to the recruiter later. Those who talk to the recruiter on the phone can either sign the study consent/assent forms and post them back to the recruiter, or scan the forms and email them electronically or sign the web based consent form provided through the University of Bristol's data capture system (Research Electronic Data Capture (REDCap, http://project-redcap.org/). Methods for obtaining consent that are not useful in this feasibility trial will not be used in the main trial.

We will ask young people and parents/carers about the acceptability and feasibility of the different methods of recruitment and providing consent during the interviews described below.

Inclusion/exclusion criteria:

Children and adolescents will be eligible for inclusion if they are given a diagnosis of CFS/ME (made using NICE guidance)[5] and aged between 8 and 17 years inclusive.

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Children and adolescents will be excluded if they are severely affected. NICE defines severe CFS/ME as individuals who are unable to do activity for themselves, or carry out minimal daily tasks only, they have severe cognitive difficulties and depend on wheelchair for mobility[5]. ; or are referred for CBT at their first clinical assessment; or are unable to attend clinical sessions. Eligibility assessment will be carried out by the clinician at assessment and confirmed by the recruiting researcher.

Screening logs will include information on every young person assessed in each centre. Screening logs will be maintained by a member of the research team in each location who will collaborate with the lead clinician. Logs will include details on whether the young person was approached to take part in the study. If the young person was not approached the reason will be recorded (e.g. clinician forgot, or not eligible). If the young person is not eligible, the reason will be recorded. Logs will not have identifiable patient data but have a research number only. The research number will be linked to the patient name and the link will be held separately in the NHS centre.

Arrangements for allocating participants to trial groups:

Once the recruiter has received the signed consent/assent form they will use the automated telephone/web randomisation service operated by the Bristol Randomised Trials Collaboration. Allocation (1:1) will use minimisation to facilitate balance by age and gender, and retain a random component to prevent accurate prediction of allocation. Because of the nature of the intervention, it is not practical to blind either the family or the clinical service of treatment allocation. If allocation is done during the recruitment appointment, families can choose to know the allocation immediately or be told later by phone or letter. If the allocation is done once consent/assent is received, the recruiter will either phone, email or write to the family (depending on what the family has chosen) with their allocation. They will inform the clinical service who will then write to the young person /family with their appointment details. GP's will be told what intervention the young person will receive as part of routine clinical practice.

Interventions*:*

Therapists treating children and adolescents in both arms will be encouraged to offer routine[5] advice about sleep, medication use and symptom control at the assessment and follow up appointments in both treatment arms.

Activity management will be delivered by CFS/ME specialists (occupational therapists, physiotherapists, nurses, psychologists). As Activity Management is currently being delivered in both services, therapists will not require further training however therapists will receive guidance on the Mandatory, Prohibited and Flexible components detailed below. Activity management aims to convert a "boom-bust" pattern of activity (lots one day and little the next) to a baseline with the same daily amount. For children/adolescents with CFS/ME these are almost entirely cognitive activities: school, school work, reading, socialising, and screen time (phone, laptop, TV, games). Those allocated to this arm will receive advice about the total amount of daily activity, including physical activity, but will not receive specific advice about their use of exercise, increasing exercise or timed physical exercise.

Mandatory: Therapists will discuss the different types of cognitive activity (high concentration and low concentration) which will vary according to age. Participants will be taught how to

find their baseline of cognitive activities. Cognitive activities include time at school or doing school work, reading, some craft/hobbies, socialising and screen time (phone, laptop, TV, computer, other devices). The baseline is the median time spent doing cognitive activity and can either be estimated in collaboration with the specialist therapist or calculated after a period of recording activity. Once the baseline is agreed with participants, they will be asked to record the total number of minutes spent each day doing high-energy cognitive activities using paper diaries or our award-winning smartphone app "ActiveME". Recording activity is used to help participants understand whether they are doing the same each day or varying their activity and whether the baseline has been set at the correct level. When participants have managed the baseline for 1-2 weeks, they will be asked to increase this by 10-20% each week[5]. Therapists will discuss problems encountered by participants and provide possible solutions.

Managing setbacks will be discussed (how much to reduce school and other cognitive activity and for how long). Participants will continue to increase activity until they are able to do at least 8 hours of cognitive activity a day.

Therapists will complete a tickbox checklist for each session to record which mandatory elements were provided.

Prohibited: Discussion about number of steps, minutes of exercise, aerobic, versus non aerobic activity. No discussion about increasing physical activity (only discussion about increasing overall activity). No advice on exercises or using a strengthening programme.

Flexible: Advice on PE in school (no PE, half a lesson, full lesson). Attendance at sporting events (do not attend, attend limited period of time). Children and young people can record physical activity within the total cognitive activity but are not required to do so.

Graded Exercise Therapy (GET) will be delivered by referral to a GET-trained CFS/ME specialist who will receive guidance on the Mandatory, Prohibited and Flexible components detailed below. Children and adolescents will be offered advice that is focussed on exercise with detailed assessment of current physical activity, advice about exercise and a programme including timed daily exercise. young people will be asked to record the amount of exercise and taught to use a heart rate monitor with target heart rates to avoid overexertion. They will be able to choose whether they want text reminders to do exercise.

Mandatory: Physical assessment, assessment of range and type of exercise used during the week at the first assessment. Functional muscle test at assessment and 6 months including: sit to stand and 2 minute walk test (distance covered). Exercise targets will be negotiated with the young people and parents/carer. Initial exercise targets (the baseline) will be the median amount of daily exercise done during the week. Once this is achieved every day for one to two weeks, participants will be advised to increase exercise slowly by 10-20% a week. They will be asked to time their exercise to make sure they are completing the same number of minutes of exercise every day and record these minutes of exercise each day using either paper diaries or our smartphone app "ActiveME". Diaries (paper or using ActiveME) will be reviewed to help children and adolescents ensure their exercise is the same every day. Once children and adolescents are doing 30 minutes of gentle exercise each day, the exercise will increase in intensity such that participants start doing aerobic exercise. The aerobic component will then be slowly increased as the total amount of exercise is increased. The exercise programme will be negotiated and agreed together at each appointment between the therapist, young person and parent/carer.

Children and adolescents aged 10 and over will be taught how to monitor their heart rate using a heart rate monitor to prevent them doing too much exercise. They will be set a target heart rate and asked not to exceed this. Younger children or those who cannot measure their heart rate will learn how to monitor their heart rate with their parents.

Managing setbacks will be discussed prior to discharge in the context of physical exercise (how much this should be reduced and when they should start to do exercise again).

Participants will be encouraged to continue to increase exercise to achieve Department of Health recommended levels of 60 minutes a day of a mixture of moderate/vigorous intensity aerobic with muscle strengthening activities on three days/week.

Therapists will complete a tickbox checklist for each session to record which mandatory elements were provided.

Prohibited: Advice on cognitive activity, discussion about the different types of cognitive activities. Instructions to record the cognitive activities.

Flexible: Assessment of range of movement. Advice on length of time at school (full days, half days, one lesson a day), support increasing time at school. Advice over exams. Participants can be shown how to do stretches. They can also be offered a strengthening programme if this is one of their goals.

Treatment delivery: In both treatment arms, participants, their parents/carers and the clinician providing treatment will choose the number of follow up sessions (estimated to be between 8 & 12) and the frequency of appointments (every 2-6 weeks), in line with standard clinical practice. We will collect the number, frequency and length of follow up sessions for each participant as well as data on heart rate monitor use. Therapist may offer appointment via skype. In this instance sessions will still be audio recorded. Participants will be asked to provide consent to the audio recording of treatment session on paper forms, to be returned by post, or on-line via the redcap system.

Participants who develop anxiety or depression that require treatment during the trial follow up period will be offered up to 12 sessions of CBT delivered as individual sessions every 2 weeks by a CFS/ME specialist psychologist.

If participants, their parents/carers or therapists feel they would benefit from the alternative treatment arm, they will be able to cross-over after 6 months (the primary outcome) and this will be recorded. Participants will be strongly encouraged not to cross over before 6 months however they are allowed to withdraw from either treatment or the trial at any time. Therefore, if participants want to cross over before three months, this decision will be recorded and they will be encouraged to continue to provide outcome data.

We will record the number of booked treatment sessions where participants Did Not Arrive (DNA) or where there was a late cancellation (within 24 hours). We will assume that the intervention is not acceptable for participants who DNA or have late cancellations for >25% of follow up appointments.

We will assume that those who did not attend (or cancelled within 24 hours) three or more consecutive appointments or 50% of appointments did not find the interventions acceptable.

Outcome measures

The primary outcome for the feasibility study is the feasibility and acceptability of investigating GET in a RCT. Patient reported outcomes are collected at baseline, 6 months and 12 months post randomisation. Baseline data is routinely collected at the first clinical assessment prior to recruitment.

Table 1: Data routinely collected at assessment. Questionnaire data also collected at 6 & 12 months.

Assessment data	**Questionnaires**
Age	Chalder fatigue[12]
Sex	Physical function (SF 36)[13]
Ethnicity (drop down list)	Hospital Anxiety Depression Scale[14]
School attendance	Spence Children's Anxiety Scale[15]

% possible school	
Symptoms List	Pain visual analogue scale
CDC & NICE criteria	Quality of life (EQ-5D-Y)
Months of illness	Clinical Global Impressions scale*
Co-morbid conditions	

*Follow up only.

Probable primary outcome measure for the full trial: We will probably use child completed SF-36-physical function sub-scale (PFS), analysed as a continuous variable, at 6 months post-randomisation as in our previous trial[16, 17].

Probable secondary outcome measures include: Child self completed questionnaires measuring: school attendance (percentage of expected sessions); Chalder Fatigue score; pain visual analogue scale, depression and anxiety (Spence Children's Anxiety Scale (SCAS) and the Hospital Anxiety and Depression Scale (HADS, if they are 12-17 years old)) at 6 and 12 months as well as the SF36-PFS at 12 months.

Participants in both trial arms will be asked to wear an accelerometer (GT3X+) to measure physical activity for seven days within one month of randomisation and at 3 and 6 months follow-up. Accelerometers will be posted to participants within 2-4 weeks of their first clinical assessment. Instructions will be included with the accelerometer and a member of the research team will phone the participant in the first week to check that they have understood how to wear it.
Accelerometers are small, match boxed sized devices that measure physical activity. They have been shown to provide reliable indicators of physical activity among children and adults [11].

The accelerometer data will be processed to identify mean minutes of sedentary, light and moderate to vigorous intensity physical activity per day using established accelerometer cut-off points and protocols[16 24] . The mean accelerometer counts per minute, which provides an indication of the volume of physical activity in which the participant engages, will also be calculated using established methods.

In the initial stage of the study approximately 10 participants will be asked to complete a log of wear time (time worn and time taken off). This wear diary data will be compared against accelerometer data to check for the validity/ reliability of using accelerometers with young people with CFS/ME.

Measurements for Health Economic evaluation: Participants will be asked to complete the EQ-5D-Y at baseline, 6 and 12 months. Both parents will be asked to complete inventories at baseline and 6 and 12 months follow up including: an adapted 6 item Work Productivity and Activity Impairment Questionnaire (General Health V2.0 [WPAI:GH])[18] and an adapted existing health resource use questionnaire to measure health service use (e.g. GP or specialist care), educational service (e.g. school counsellor) and travel costs. We have tested the acceptability of these inventories in this participant group. We will extract information from the specialist services medical records to identify referrals for additional CBT or referrals to Child and Adolescent Mental Health services within 12 months of randomisation.

Follow up

We will email participants to complete outcome measures at 6 months and 12 months with a link to the questionnaires on REDCap. If families do not have internet access at home, we will post questionnaires. If outcomes are not completed, an email reminder (or postal reminder if they do not have internet access) will be sent after one week. If outcomes are still not completed a further email (or postal) reminder will be sent with a link to a reduced number of questions containing just the Chalder Fatigue Scale and the SF-36 PFS. If this is

not completed we will make up to four follow up telephones calls or emails and offer to collect the primary outcome data over the phone. We are currently using this system for collecting outcome data in our NIHR funded observational cohort.

Integrated qualitative methods

Qualitative research methods will be integrated into the feasibility study to optimise the recruitment process and investigate acceptability of the interventions and wider trial processes. The research will be flexible in its intensity and comprehensiveness depending on the type of issues that emerge. Sources of difficulties will be fed back to the CI and trial management group and suggestions made to change aspects of the design, conduct, organisation or training that could then lead on to improvements in how the feasibility study is conducted.

Exploring issues with trial processes: The recruiter will receive a two hour training session on the two treatment arms and be provided with information on providing balanced information to children and young people. To identify recruitment difficulties and improve recruitment[10] we will audio-record (with consent) all recruitment consultations. The research team will analyse the recruitment consultations regularly documenting the interaction between recruiter and potential participant and explore information provision, recruitment techniques, patient intervention preferences, and trial participation decisions. If analyses of the audio-recordings suggest that any recruitment difficulties are being caused by the recruitment consultation, training will be offered with the recruiter . This may include simply providing feedback on the recruitment consultation or may include suggestions on how to make the consultation more balanced in terms of information given on the different interventions.

If the number of eligible patients recruited are lower than expected or if there are differences in the percentage recruited between centres, we may undertake in-depth interviews with members of the clinical and recruitment staff and analyse screening logs to examine problems with patient pathways in the different centres.

We will undertake in-depth interviews with parents/carers and their children to understand their views and experiences of trial processes.This will include: provision and acceptability of patient information and reasons for accepting or declining participation. We are particularly interested in understanding barriers to participation and will interview (subject to informed consent) those who choose not to participate in the trial, who drop out of trial follow up or who do not accept treatment allocation at randomisation.

We will interview young peopleand their parents about their use of the accelerometer, whether it is an acceptable device to wear and whether there are particular issues we need to consider in this patient group for the full trial.

Intervention sessions will be routinely audio-recorded, with consent to enable us to: test that the two treatments are truly distinct and ensure treatments are delivered in a consistent manner across centres. To monitor protocol adherence, two clinicians, from centres other than that in which the session was delivered, will listen to a random sample (~10%) of the audio-recorded sessions and rate them on a 5 point likert scale as being GET or Activity Management or a mixture of the two using the Mandatory, Prohibited and Flexible elements for each intervention described above. Clinicians will be blinded to whether the recording is from a GET or AM intervention.

The delivery of up to 10 interventions, in both arms in each centre, will be observed. Sessions delivered early in the feasibility study will be observed initially, with further sessions being sampled depending on analysis of these initial observations. Detailed notes will be taken, including the context, intensity and variability of intervention delivery, to understand how interventions are delivered and received in practice and help interpret outcomes (for example, variation between subgroups).

We will interview parents/carers and their children about both interventions including any prior exposure to the study treatments; beliefs, expectations and preferences about the treatments before assignment; their experiences and acceptability of the treatments; use of heart rate monitors (including whether they increase or decrease anxiety); and their views of the number of treatment sessions required. Participants will be recruited from both centres to assess differences in implementation between settings.

We will interview clinicians delivering both treatments in each centre to ascertain their views on: the feasibility of delivering the intervention to participants (particularly focussing on younger children); changes that need to be made to the interventions offered; engagement, compliance and technical problems with using heart rate monitors and accelerometer; and optimal frequency of interventions.

Sampling for interviews will ensure that a range of informants (in terms of age, gender, ethnicity, geographical location, socio-economic circumstances, and disease severity) are included (maximum variation sampling), and that people with particular characteristics of interest can be targeted to follow-up and develop emerging findings (theoretical sampling). Interviews will be semi-structured using a topic guide to ensure interviews cover the same issues while allowing new issues of importance to emerge. All interviews will be audio-recorded with consent using encryption software, transcribed verbatim and anonymised.

Sample size for interviews will be determined by data saturation, i.e. when no new themes are being uncovered. It is anticipated that up to 20 patients, 15 parents, and 10 practitioners will be interviewed at a location of their choice. We estimate that a sample size of 45 will be sufficient to determine: feasibility, acceptability, the appropriate number of follow up sessions, paper/web based collection of outcome measures (or both) and collect sufficient information to determine the sample size for a full, adequately powered study.

Interviews will take place in clinic, in the participant's home or via Skype. If interview take place over Skype participants and parents will be asked to provide consent on paper forms, to be returned by post, or on-line via the redcap system.

Sample size for feasibility trial

An estimated 330 children and adolescents are assessed per annum in the two centres (Bath/Bristol 300, Newcastle 30). Estimates based on the SMILE trial suggest 60% will be eligible, of which 40-50% will be recruited. We therefore estimate that recruitment will take approximately 12 months.

We believe a sample size of ~100 participants will provide sufficient information to inform a full trial. Recruiting 100 participants from 430 eligible young people approached will give a 95% confidence interval of 20-28% for an estimated recruitment rate of 24% (0.6 eligible x0.4 consenting), which is acceptably precise for planning the main study recruitment.

ANALYSES

Recruitment (Objectives 1 and 2)

We will analyse the recordings of the trial recruitment appointment by the recruiter as well as the interviews with young people and parents, clinical and recruitment staff about the recruitment process.

Analysis will be ongoing and iterative commencing soon after data collection and will inform further sampling and data collection. Interview transcripts will be imported into NVivo, systematically assigned codes and analysed thematically to identify themes using techniques of constant comparison. Individuals exhibiting contrasting attitudes ('negative cases') will be studied in detail. The perspectives of the individuals will be paramount, with careful account taken of the context within which the discussion takes place. Data analyses will primarily be undertaken by the applicant and the qualitative researcher. To check coding

reliability, other members of the team will independently analyse a proportion of transcripts and compare findings.

Content analytic methods will be used to describe in a structured manner what was said by whom and how often in the audio-recordings of recruitment sessions. More flexible grounded theory methods will be applied to identify common or divergent themes, particularly focusing on the impact of statements by the recruiter on patients. Conversation analysis will be used to focus in great detail on certain sections of the transcripts, for example, in the interactions during which randomisation is offered.

We will calculate the percentage recruited of those eligible using screening logs. When the recruiter has told young people and parents what their allocation is, the recruiter will ask whether they accept that allocation. We will record the number who do not accept the allocation at randomisation and the number who do not find treatment acceptable (those in who DNA or cancel late >25% of appointments). We will combine these with qualitative data from the interviews where patients discuss the acceptability of the trial methodology to determine the feasibility and acceptability of a full trial.

Findings will be fed back to the CI and trial management group with suggestions on how to optimise recruitment to the feasibility study. Numbers of eligible patients, and the percentages of these that are approached about the trial, consent to be randomised and immediately accept or reject the allocation will be assessed before any feedback or training is given, and regularly afterwards to check whether rates are improving.

Retention (objective 3)

At the end of the feasibility phase (12 months) we will calculate the percentage of recruited participants who provide 6 month data to estimate retention. We estimate that approximately 40 (40%) of those recruited during the 12 months of this study, will have had the opportunity to provide 6 month follow up data. The remainder will provide follow up data if this proceeds to a full trial. This will allow us to estimate completeness of follow up. We will explore the qualitative data to look for themes that may affect retention.

Acceptability of GET and AM (objective 4**)**

We will analyse data collected during interviews with young people and their parents to understand whether Graded Exercise Therapy and Activity Management are acceptable interventions (see analyse methods above). We will estimate the proportion of participants who found the interventions acceptable in each arm by assuming that those who DNA at appointments or cancelled appointments within 24 hours did not find the interventions acceptable.

Feasibility and acceptability of accelerometer measurements (objective 5)

We will record the percentage of participants who wear the accelerometers and provide useful data and their views (and those of their parents) on the acceptability of the devices. We will review wear/non-wear logs in the interview and use these to discuss issues over either feasibility or acceptability of wearing the accelerometers.

If the feasibility trial goes to a full study, we will use data collected from accelerometers to quantify physical activity levels in both trial arms and examine whether changes in activity mediate or are associated with outcome. To enable us to understand whether we will be able to obtain useful data, we will analyse accelerometer data as follows: Periods of ≥60 minutes of zero values will be defined as accelerometer “non-wear” time and discarded. Participants will be included in the analysis if they provide ≥2 weekdays of data with at least 500 minutes of data between 6am and 11pm. We will sample 10 young people and ask them about periods which appear to be “non-wear” time to check whether this is non-wear or sedentary behaviour.

Mean minutes of weekday, light and moderate-to-vigorous physical activity (MVPA) per day will be established for weekdays using the threshold developed by Evenson and colleagues[19], which has been shown to be the most accurate for this age group[20]. The mean number of accelerometer counts per minute (CPM), which provides an indication of the overall volume of activity in which young people engage, will be calculated.

Fidelity of GET and AM (objective 6)

We will analyse data collected from clinicians and calculate the percentage of sessions in each arm that were rated correctly by the two clinicians (as GET or AM when that was the session given) and the percentage where clinicians were uncertain or said that the session was a mixture of both treatments as well as the percentage rated as GET when it was in fact AM and or vice versa.

We will also review transcripts and observation notes from the observed treatment sessions observed and determine if they complied with each intervention using the Mandatory, Prohibitory and Flexible elements described above.

Health Economic analyses

We will assess the feasibility of using routine data to gather information on the initial costs of the GET and activity management interventions and other specialist services (e.g. CBT) offered to particpants. We have already evaluated our health resource use questionnaires in the SMILE trial and will test the acceptability of using these measures at 6 and 12 months to estimate the other CFS/ME related costs to the NHS, other government agencies and the broader impact on family expenses, productivity and informal care.

Proposed Stop-Go-Amend criteria for MAGENTA & safety outcomes

Proposed Stop Criteria for MAGENTA: We will not proceed to the full trial if at 12 months (end of August 2016), one of the following is true:

1. We have recruited less than 70 participants (~70% of the target specified) AND if the qualitative data collected suggests that we cannot improve recruitment by changing recruitment methods
2. The 6 month follow up is less than 80% and AND if the qualitative data suggests we cannot improve follow up.
3. The qualitative data suggests the interventions are not acceptable to young people and/or their parents.
4. If the DSMC recommend the trial is stopped for safety reasons and if the TSC agree with this decision.

Safety Outcomes

For *safety outcomes* we will prospectively collect serious and non-serious adverse events defined as any clinical change or illness reported at clinic or postal follow up. We will define a serious deterioration in health as: a decrease ≥20 in SF-36-PFS or scores of “much” or “very much worse” on the Clinical Global Impression scale; clinician-reported serious deterioration in health; or withdrawal from treatment because of feeling worse. Safety outcomes will be analysed by the Data and Safety Monitoring Committee (DSMC) and reported to the Trial Steering Committee.

Frequency of analyses: The first interim safety analyses will be at 10 months (before the trial transitions from the feasibility to full phase). The DSMC will decide on the second safety analyses which may be at 18 months or when 50% of partcipants have been recruited. The safety analyses will be used to ensure that neither intervention arm is having a detrimental effect. These analyses will only investigate safety outcomes and will be conducted by an independent statistician with results provided to the Data and Safety Monitoring Committee.

Data and Safety Monitoring Committee (DSMC): (3 independent experts in CFS/ME, statistics and trials) will have unblinded access to the data to make recommendations to the TSC on whether there are safety reasons to stop the trial.

Storage of data and data protection

Children and young people are allocated a unique 7 digit research identification number. This number is assigned to the patient and is used on clinical assessment forms prior to transfer of data so they are anonymised at source. A list of names and corresponding identification numbers are kept separately and securely on a password protected NHS server. This number will be used on screening logs and on all data collected. Personal information will be kept on consent forms which will have contact details. Consent forms will be kept within a locked filing cabinet in a locked office within the University of Bristol.

Data will be entered into REDCap a secure system used by multiple institutions for large multicentre studies. Assessment data will be entered by the research team as this is collected prior to assessment. Participants will be encouraged to provide follow up data using REDCap but will be able to provide data by post if they do not have internet access. Participants are required to log in to the system and have to pass authentication before they can access their own data. There are several authentication methods available. The University of Bristol will use table-based authentication, which utilizes the storage of username/password pairs in a database table. In this system, the password in the database table is encrypted as a one-way hash of the password. Participants will be sent a web link to REDCap which will only allow access to their data. They will create a password which they will use each time they log in. REDCap also has an auto-log out system that will log participants out after 30 minutes if they have stopped using the database.

Audio-recordings will be encrypted, password protected and stored on a secure university server for five years. This is to enable us to check recordings if necessary while reports are being written. Transcripts will be anonymised and secure password protected university server.

Withdrawal from the study

Participants can withdraw from the study at any time without giving a reason. If a participant wants to withdraw from the study, they will be asked to inform the MAGENTA project manager. We will retain non-identifiable information already collected from participants but will ask whether they want to withdraw from the intervention, further data collection or both.

Ethical Issues

Graded Exercise Therapy, Cognitive Behavioural Therapy and Activity Management are recommended as a treatments in NICE guidance[5], however there is no evidence that Graded Exercise Therapy is effective or safe in young people. CFS/ME is different in children/adolescents and adults with different risk factors, course and outcome[21]. It is therefore not possible to extrapolate the results from adult studies to children/adolescents. A trial in children and adolescents is therefore needed.

At the moment, CBT has the best evidence for treatment efficacy. We have not included CBT as the control arm because clinicians would not be in equipoise in randomising participants to CBT or GET. This is because currently, clinicians recommend CBT at assessment for those who present with CFS/ME and co-morbid mood problems. We have ensured that CBT continues to be a treatment option for young people who develop mood

problems after randomisation and can be accessed in addition to either treatment arm. We will analyse the use of CBT as a secondary outcome using hospital records.

Because the participants will be children and adolescents, we have put in place rigorous procedures for informed consent from parents and guardians on behalf of their children. We will also ensure we have informed consent/assent from participating children and young people. In the clinic, the clinician will ask for consent/assent for contact by a recruiter and qualitative researcher. Consent/assent to the study and to randomisation will be obtained by the recruiter after a full explanation of the study when both the young person and the family have had sufficient opportunity to ask questions. Young people and their families will be given as long as they need before giving consent/assent within the confines of the study. We will then obtain further consent/assent prior to each interview to check that young people or their parents continue to be willing to participate. We will also obtain consent/assent prior to recording any interventions from all present.

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