



Clinical
Trials
Research
Unit.



Hydrotherapy for Duchenne muscular dystrophy (DMD): a pilot and feasibility randomised controlled trial in children

Hydrotherapy for DMD Research Protocol

Version: 6, 18Nov15

REC reference:

HTA reference: 12/144/04

ISRCTN NUMBER:

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1.0 Lay Summary

Duchenne muscular dystrophy (DMD) is a rare disease mainly affecting boys. DMD causes muscle cells to gradually break down so that with time, a patient's muscles become weak to the point where they are unable to conduct many of the activities they used to. There is no cure for this disease, but doctors and physiotherapists try to slow down its progression and the development of complications by prescribing steroids and a physical management programme. Clinical experience shows that physical activity helps to maintain functional abilities. Mostly physical management programmes are done on dry land. However they can also be performed in warm water, under supervision by a physiotherapist; this is known as 'hydrotherapy' or 'aquatic therapy'. Hydrotherapy enables affected people to perform exercises which may not be possible on land due to the support provided by the water. Additionally the activity is seen as fun for them and their carers. Despite this, hydrotherapy is difficult to access in many places in the UK. Many NHS trusts do not fund it or have not got the facilities to offer it.

While we know people with DMD value hydrotherapy, we are not sure whether it really adds anything to land-based exercises alone in terms of helping with walking and other daily activities. We are therefore undertaking a small scale pilot study to help decide if a larger scale trial would be feasible and if so, how we should best conduct it. We plan to recruit 40 boys with DMD in the UK within 4 to 6 sites. Equal numbers will be allocated at random to either receive hydrotherapy plus land based physiotherapy (active intervention group) or land based physiotherapy alone (control group). Study participants will be assessed for key outcome measures at 3 time points: consent and screen 1 visit; baseline visit; 26 week visit. We will collect information on a number of outcomes relating to the feasibility of conducting the trial which will include interviews with study participants in both groups. We will also collect information about the health of boys - how mobile they are, how independent and active they are and what their quality of life is like. Data relating to the cost of the hydrotherapy to the NHS and to carers will also be gathered.

The project is funded by the HTA (Health Technology Assessment) Programme.

GENERAL INFORMATION

Sponsor

Gillian Gattenby
Clinical Research Facility
Sheffield Children's NHS Foundation Trust
Western Bank
Sheffield
S10 2TH
Tel: (0114) 3053219
Fax: (0114)
gillian.gattenby@sch.nhs.uk

Chief Investigator

Dr Peter Baxter
Sheffield Children's NHS Foundation Trust
Western Bank
Sheffield
S10 2TH
Tel: (0114)
Fax: (0114)
p.s.baxter@sheffield.ac.uk

Clinical Trials Support and Management

Chin Maguire
Clinical Trials Research Unit
The University of Sheffield
School of Health and Related Research
30 Regent Street
Sheffield
S1 4DA
Tel: (0114) 222 0717
Fax: (0114) 222 0870
c.maguire@sheffield.ac.uk

2.0 BACKGROUND (detailed justification for the trial including)

Duchenne muscular dystrophy (DMD) is an inherited muscular disease mainly affecting boys which is characterized by the progressive break-down of muscle fibres leading to loss of strength and functional abilities. With no cure, the primary aim of management is to preserve physical function, activities of daily life and quality of life. Physiotherapy is a key aspect with the aim of delaying the progression of weakness and secondary complications such as contractures. Based on limited research evidence and clinical consensus, international guidelines currently adopted in the UK Bushby et al (2010) recommend a range of voluntary age-appropriate activities for ambulatory boys, suggesting "regular submaximum (gentle) functional strengthening/activity, including a combination of swimming-pool exercises and recreation-based exercises in the community." Hydrotherapy is supervised exercise in warm water. The water decreases loading of joints through buoyancy and can provide graded resistance to movement through the use of turbulence. For those with more severe levels of disability exercise in the water can permit levels of function and physical training that are no longer possible on land. Despite the high value which people with neuromuscular disorders place on hydrotherapy, its provision for people with DMD is uneven, with regions where it is unavailable due to a lack of facilities, absence of funding, or both. Reversal of this trend, in a climate of fiscal constraint, is likely to require evidence from well-conducted randomised trials and economic evaluations, but none is available at present.

This pilot and feasibility trial aims to recruit children and young people with Duchenne muscular dystrophy (DMD) who still have some mobility. One group will be randomized to receive hydrotherapy and optimized land based exercises while the other receives optimized land based exercises alone. The study is designed to address the specified outcomes, ability to recruit; acceptability of treatment (ability to randomise); maintenance of mobility / independence / activity; and costs. In addition it will assess the possible treatment effect, to allow a power calculation for a main trial; attrition and the reasons behind attrition; intervention fidelity; quality of life; and adverse effects of the intervention. The Brief also specified a 12 month follow up but in the feedback from the preliminary application we were requested to shorten it to 6 months. As at present there is no agreed exercise protocol for boys with DMD, nor any agreed hydrotherapy protocol, a group including senior colleagues in the therapy and medical fields with experience in treating boys with DMD have drafted detailed guidelines for both.

There is no high quality evidence suggesting that hydrotherapy confers a clear health benefit (narrowly defined) in DMD. Possible benefits may include improved joint range, maintenance of muscle strength, improved options for exercise and play as well as maintaining respiratory ability. The intervention aims to prolong independent function and mobility on land, which has benefits for parents / carers. Defined more widely, there is widespread anecdotal evidence that hydrotherapy provides options for exercise, play and social interaction with a peer group not always available to young people with a life-limiting disease. At a societal level, the information collected in this study can inform evaluations of whether this utility gain is real and whether hydrotherapy is cost-effective at standard willingness to pay thresholds.

There are no articles specifically reporting studies of aquatic or hydrotherapy for DMD. Getz et al found 11 articles in a systematic review of the literature relating to aquatic interventions in children with neuromotor impairments (Getz, 2006). The 2 articles concerning children with spinal muscular atrophy were of level IV and V evidence (the latter was a case report) and both showed an improvement in activities of daily living. One level IV article in 3 children with undefined progressive muscular dystrophy reported an improvement in respiratory function. The other studies concerned children with cerebral palsy. None of the articles reported negative effects due to aquatic interventions.

In children with other long term disabilities that are not primarily of muscular origin, there is little data about hydrotherapy. In a review of aquatic therapy in children and adolescents with cerebral palsy, Gorter & Currie also found poor study quality and no strong supporting data (Gorter, 2011). There have also been a number of articles relating to juvenile idiopathic arthritis, the most comprehensive of which is the NIHR HTA-funded randomised controlled trial (RCT) study by Epps et al into the cost effectiveness of hydrotherapy, which compared an intensive hydrotherapy programme with one of land-based exercise and found no overall benefit from hydrotherapy (Epps, 2005). Most reported studies are limited by small numbers, inadequate design (eg case series, lack of control group etc), risk of bias, and vary in terms of intensity and duration of the intervention.

Studies suggest that boys with Duchenne demonstrate improving physical abilities until, on average, 7 years of age (6 minute walk test). They generally demonstrate a plateau in physical function followed by a variable decline in physical abilities dependent upon their clinical management and disease progression in the individual. The target population will be ambulant boys aged 7-16 years with genetically confirmed DMD who attend one of the participating clinical centres for management and review. Assessments will be undertaken by the specialist neuromuscular physiotherapists employed by participating centres.

In conclusion, whilst there is some, generally low grade, evidence in the literature relating to the benefits of aquatic or hydro-therapy for children with long-term conditions, there is none relating to DMD specifically. Given the particular nature of the pathology it is not appropriate to extrapolate findings from other articles in hydrotherapy to this patient group.

3.0 TRIAL DESIGN, OBJECTIVES AND PURPOSE

Study design: parallel group, open labelled, randomised pilot feasibility trial with nested qualitative research. Although the physiotherapists, physicians and participants will not be blinded, the Health Economist and Statisticians will remain blinded to treatment allocation.

Summary of treatments

Participants will be allocated on a ratio of 1:1 using simple randomisation with permuted blinded block size to:

1. Control group to receive optimised land-based exercises (n=20);
2. The intervention group will receive the same plus hydrotherapy (30 min, twice weekly, for 6 months: active assisted and/or passive stretching regime; simulated or real functional activities; sub-maximal exercise) (n=20).

More detail on the interventions is given below.

Full details of both interventions are given in section 4.4.

Primary objective

Determining the **feasibility of recruitment** to the main trial is the primary objective of the study (recruitment of 40 participants in 6 months from 4 centres with 2 in reserve).

Secondary objectives

The secondary outcomes are separated into 2 groups: feasibility outcomes and clinical outcomes

FEASIBILITY OUTCOMES

1. Decision on the primary endpoint for the main trial (current estimate suggests 80% power, two-sided, with n=610 to detect 5% [18m] difference in 6 min walk test with 10% dropout at 12m);
2. Number/characteristics of eligible patients approached for the study
3. Reasons for refused consent
4. Participant attrition rate;
5. Reasons for attrition;
6. Participant views on acceptability of research procedures and intervention;
7. Number of missing values/incomplete cases;
8. Feasibility of recruiting participating centres and estimation of costs;
9. Intervention fidelity;
10. Therapist views on intervention/research protocol acceptability/perceived contamination of control arm.

CLINICAL OUTCOMES

The following will be assessed during routine clinical visits at baseline and 6 months (* indicates routine assessment):

1. Six-minute walk test (McDonald, 2010);
2. North Star Ambulatory Assessment* (measures of functional exercise capacity) (Scott, 2012; Mayhew, 2011);
3. Forced Vital Capacity (FVC)*;
4. Child Health Utility 9D Index (health state utility for economic evaluation) (Vandervelde, 2007);
5. ACTIVLIM (measure of independence and activity) (Stevens, 2011);
6. CarerQoL (carer burden) (Brouwer, 2006);
7. Health and social care resource-use questionnaire (cost data for economic evaluation).

The following safety outcomes will be assessed at hydrotherapy session for those in the intervention arm only after each hydrotherapy session:

1. Pain (visual analogue scale)
2. Children's OMNI Scale of Perceived Exertion (Robertson, 2000)

Table 1: Clinical outcomes

	Consent and Screen 1 visit (minus 4 weeks)	Baseline	At each Hydrotherapy session	26 weeks post randomisation
ALL PARTICIPANTS				
1. North Star Ambulatory assessment (routine)	✓	✓		✓
2. 6 minute walk test		✓		✓
3. Forced Vital Capacity (FVC)		✓		✓
4. ACTIVLIM		✓		✓
5. Child Health Utility 9D Index		✓		✓
6. CarerQoL		✓		✓
7. Health and social care resource use questionnaire		✓		✓

HYDROTHERAPY ARM ONLY				
8. Pain (visual analogue scale) – before and after each session			✓	
			✓	
9.. Children OMNI Scale of perceived exertion – before and after each session			✓	

4.0 **SELECTION OF SUBJECTS**

Four centres have been screened for their ability to recruit and these sites, have easy access to hydrotherapy. There may be a need to increase the number of sites- up to a maximum of 6 – should recruitment be slow. All centres have identified a sufficient pool of eligible patients and confirmed that they expect to be able to recruit 10 patients in the six month accrual window (during which all patients would have one routine clinic visit), notwithstanding size of catchment area. We expect a consent rate of 50% of those screened as eligible, with the generally poor access to the kind of intensive hydrotherapy offered as part of this research protocol providing a strong incentive to participate.

4.1 Inclusion criteria

1. Genetically-confirmed DMD; A muscle biopsy report from a registered NHS pathology laboratory showing dystrophin deficiency compatible with Duchenne; **AND/OR** a report from a registered NHS molecular genetics laboratory showing the DMD gene to have a pathogenic deletion, duplication or point mutation.
2. Age 7-16 years
3. Established on glucocorticoid corticosteroids (patient has been treated with prednisolone or deflazacort for at least six months with no major change in drug, dosage or frequency for at least three months before the initial assessment);
This is defined as:
* Frequency is a change from daily to alternate day or other non-daily regimen (or vice versa)
* Dose increase in line with weight is acceptable. Other changes are an exclusion criterion
* Drug changes from prednisolone to deflazacort (or vice versa) is an exclusion criterion
4. North Star Ambulatory Assessment (NSAA) ≥ 8 up to 34. Exclude those with more than a 20% variation between baseline screens four weeks apart (at pre-screen and initial assessment);
5. Able to complete a 10 metre walk test with no walking aids or assistance.

4.2 Exclusion criteria

1. Involvement in another randomised controlled trial
2. More than a 20% variation between screening and baseline North Star Ambulatory Assessment scores
3. Unable to commit to the programme of twice weekly hydrotherapy for 6 months
4. Any absolute contraindications or precautions to hydrotherapy listed in table 2 below at the point of determining eligibility:

Table 2: absolute contraindications and precautions to hydrotherapy

Absolute contraindications	Precautions
Severe cardiac failure	Fear of water

Resting angina	Behaviour problems that prevent participation in physio or hydrotherapy
Shortness of breath at rest	Hypo/hypertension
Renal failure	Chemical sensitivity
Proven allergy to chlorine or bromine	Indwelling catheter/peg tube
Uncontrolled epilepsy	Tracheostomy
Uncontrolled faecal incontinence	Poor skin integrity/open wounds
Febrile conditions – acute systemic illness or pyrexia (until resolved)	Unstable angina, cardiac arrhythmias or additional cardiac considerations
Acute vomiting/diarrhoea (until resolved)	Dizziness/vertigo
Wound infection (until resolved)	Diabetes
Weight in excess of available pool evacuation equipment	Thyroid problems
	Widespread MRSA (until resolved)
	HIV/AIDS
	Haemophilia

5.0 SUBJECT RECRUITMENT and follow up

5.1 Screening and consent

Research physiotherapists/ nurses at participating sites will be responsible for identification of potentially eligible participants for the trial via screening their health records. Any possible participants with absolute contraindications will be excluded at this stage, with the reason recorded. A cover letter and information sheet will be sent to introduce the trial to the carers of potentially eligible patients. The carers will be invited to discuss the trial in more detail by telephone. The opportunity to ask further questions will be provided and, if interested an appointment will be booked at the clinic (site) for the participant and carer to attend the first visit (**consent and screen visit 1**). At this visit participants and their carers will be invited to ask any further questions about the research prior to completing the consent process:

1. Full written consent from the participants' carer
2. Full written assent from the participant

An NSAA will be completed and this data captured on the case report form (CRF) at the visit. An appointment will be made to see the participant in approximately 4 weeks' time for the **eligibility and baseline visit (visit 2)**. As NSAA and FVC are both routine measurements (completed each time participants attend clinic) NSAA or FVC completed up to 4 weeks prior to consent can be used, as data for "visit one"; baseline and eligibility (visit 2) will be conducted 4 weeks from this time point.

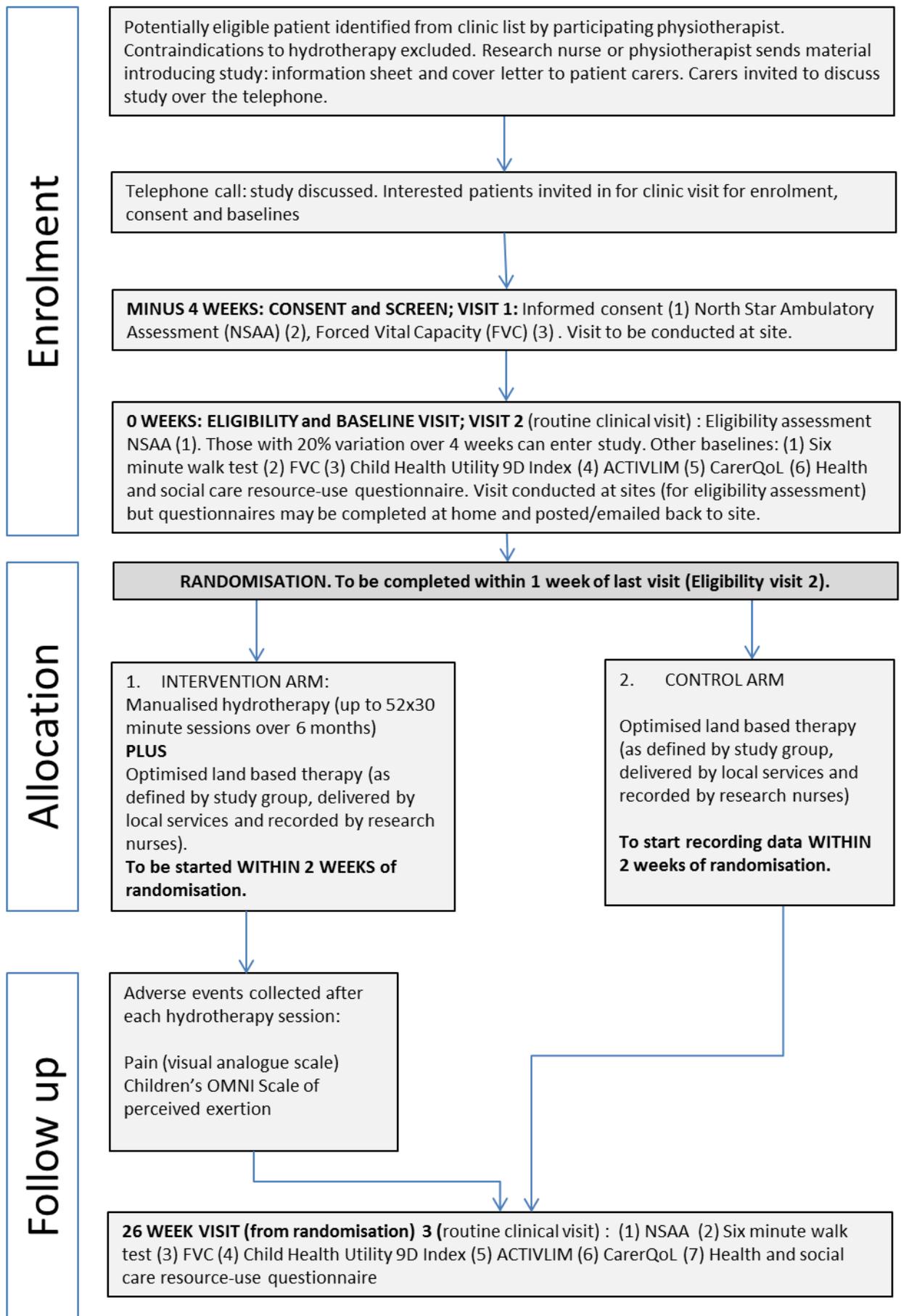
5.2 Assessment of eligibility

Tests to check participant eligibility (including repeat NSAA) will be conducted at visit 2, together with an FVC measurement. The visit will be performed 4 weeks (-/+ 1 week) from the date of the last NSAA reading taken at Visit 1. The research physiotherapist will determine at the visit whether or not the participant is eligible for the trial and complete the eligibility section of the CRF. Baseline data (questionnaires) will be collected from both participants and their carers and a 6 minute walk test will be completed at this visit. Questionnaires will either be completed at the visit or taken home to complete and be emailed/posted back to the central team.

5.3 Randomisation

If the participant is eligible, a member of the study site team e.g. physiotherapist will be responsible for randomising them to the study within 1 week of the eligibility assessment visit (visit 2). Participants will be allocated on a ratio of 1:1 using randomisation stratified by centre with randomly permuted blinded block sizes. Patient details (e.g. date of birth, other baseline criteria) will be entered into the CTRU web-based randomisation system and the treatment allocation will be returned. The participant will be informed of their treatment allocation within a week of randomisation either by phone or letter from a member of the research team at the site and their GP will be informed by post. The physiotherapist will have prescribed the exercised they deem appropriate on the land based therapy proforma at the clinic visit. This will be given to the participants (in each group) to take away. Equal number of participants will be randomised to each of the study arms at each of the sites. Figure 1 below outlines the flow of participants through the study.

Figure1: Participant flow in the trial



5.4 Trial Interventions

The trial interventions will begin **within two to four weeks** of the date of randomisation (for both intervention and control groups). The intervention descriptions given below are based on the Template for Intervention Description and Replication (TIDieR) checklist (Hoffman, 2014).

1. Intervention

Name: Hydrotherapy program

Why: please refer to the background section page 4-5

What, how: The face to face hydrotherapy programme will utilise the properties of water – buoyancy, turbulence - will include

1. Active assisted and/or passive stretching regime that targets key muscle groups in ambulatory boys – e.g. triceps surae complex, hamstrings, hip flexors, iliotibial tract, long finger flexors
2. Simulated or real functional activities e.g. sit to standing, running, jumping, hopping
3. Sub-maximal exercise in the water

A manual has been developed giving specific detail of recommended aquatic exercises to be given to each individual. This will provide a ‘menu’ of exercises from which the treating physiotherapist can choose options appropriate to the child’s level of ability and particular presenting clinical problems. Details of the hydrotherapy prescribed for the participant will be entered onto the patient’s care plan/ hydrotherapy proforma. The actual hydrotherapy activity the participant has undertaken will be recorded on the hydrotherapy proforma. Details of the proforma will be available on the HydroDMD study website.

Who provided: The research physiotherapists at the site will be responsible for booking participants into sessions for those randomised to the hydrotherapy arm and for supervising their treatment regime throughout the study. The physiotherapist may work in the tertiary paediatric neuromuscular centre or have close working links with such a centre. The intervention will be delivered by a suitably qualified physiotherapist who has experience in both aquatic therapy and the management of DMD. A training video for those providing aquatic therapy will be developed and key members of staff from each site will be invited to attend a hydrotherapy training session prior to starting participant recruitment.

Where: Hydrotherapy will take place in a suitably accessible hydrotherapy pool based in the NHS or a Special School. The pool should be heated to a temperature of 34-36°C.

When, how much, tailoring: The intervention is to be delivered twice a week for a maximum of 20-30 minutes per session in the water (to avoid fatigue) for a period of 6 months. The specific exercises will be tailored to the individual participant (see what/how above). We will measure “receipt of intervention” and “the number of sessions attended” as an outcome of the study therefore failure to attend twice weekly sessions over 6 months will not be classified as a protocol non-compliance.

How well: An external assessment will be made to consider whether the prescription of hydrotherapy represents the optimal level of therapy for each participant. This will form part of the intervention fidelity sub study outlines in section 7.0 below.

To avoid excessive fatigue, on days that participants receive hydrotherapy they will be asked not to undertake their land based therapy.

5.5 26 week follow up

The 26 week visit will be performed 26 weeks (-/+ 2 weeks) from the date of Visit 2. Outcome data collected at this visit includes a 6MWT, FVC and patient reported outcomes (see participant flow diagram above).

2. Control

Name: Land-based exercises

Why: please refer to the background section page 4-5

What, how: Land based therapy will be based upon a normal physiotherapy intervention. A comparable manual for land based exercises has also been developed. This again will provide a 'menu' of exercises from which the treating physiotherapist can choose options appropriate to the child's level of ability and particular presenting clinical problems. Physiotherapy intervention/prescription will depend upon the individual patient, however, best practice advocates:

- A regular stretching regime (4-6 days /week) and would target key muscle groups in ambulatory boys – triceps surae complex, hamstrings, hip flexors, iliotibial tract, long finger flexors.
- There is also a need to avoid disuse atrophy, whilst being aware of the potentially detrimental effects of over-exercising, particularly activities which promote eccentric activity. Therefore:
 1. A directed programme of exercises dependent upon the individuals need is prescribed
 2. General advice on regular activity is also recommended e.g. walking, cycling and swimming.

Who provided: Boys randomised to the land-based exercises only will be managed by both their research and local community physiotherapists.. Generally exercise programmes for these children are planned and monitored by a paediatric physiotherapist working in the local community and undertaken by the family, carers or a support worker in the school. Within this trial, the research physiotherapist will prescribe the land based physiotherapy prescription for the boys on the land based therapy (LBT) physiotherapy proforma and inform the community physiotherapists the combination of exercises prescribed.

Where: Land based exercises will take place as per routine clinical practice at the participants home, in the community.

When, how much, tailoring: The therapy prescriptions will normally be given face-to-face and will typically be updated every 2-3 months dependent on rate of functional change. Participants in both groups will be asked to complete the land based therapy proforma on a weekly basis over the 6 month period indicating the number of days they have completed each exercise. The number of sessions, schedule, duration and intensity will be based on the child's level of ability and particular presenting clinical problems. The children will be provided with self-addressed envelopes in order to post back their completed LBT proforma's to the central University of Sheffield team. Alternatively, they can hand these in to their research/ community physiotherapists. They will also be asked to take their LBT prescription to any visits they have with the community physiotherapist. The community physiotherapist will be asked to note any changes they make to the prescription on the LBT form. The community physiotherapist may collect this data from the participants based on their routine clinical appointments. Research physiotherapists will send out reminders to participants who have not sent

back the LBT proforma. A maximum of 3 reminder letters may be sent to participants over the course of 6 months involvement in the trial.

How well: An external assessment is planned to consider whether the prescription of land based therapy represents the optimal level of therapy for each participant in both arms of the study.

5.6 Withdrawal of subjects

Participants are free to withdraw from the study or the intervention at any time. Primarily this will be based on the participant's choice. The PI at the site may also choose to withdraw a participant from the intervention or study based on clinical need. Participants withdrawn from treatment due to clinical reasons will remain in the study and data will be collected at planned follow up time points till trial participation ends. For those who withdraw from the study entirely data already collected up to the point of withdrawal will be used in the final analysis. A member of the research team at the site will ask the participant if they are still happy to contribute data to the primary outcome.

6.0 QUALITATIVE INTERVIEWS

6.1 RESEARCH TEAM AND REFLEXIVITY

Interviewers: Two research team members, including one co-applicant (DH) and another staff member of CTRU will conduct the interviews.

Relationship established: No relationship will be established with interviewees prior to commencement of the qualitative sub-study.

Participant knowledge of the interviewer: Participants will be informed of the purpose of the research and the professional identity of the interviewer via the information sheet.

Interviewer characteristics: Interviewers are health services researchers with no motivational interest in either the population or the interventions.

6.2 SAMPLE

Sampling: Convenience samples of children and their parents on the one hand and interventionists will be taken (physiotherapists delivering hydrotherapy)

Method of approach: The consent of children and their parents will be sought by the research physiotherapist / research nurse or other health professional at the same time as RCT consent, but will not be a pre-condition of the trial entry. Interventionists will be informed at site initiation and approached by a member of the research team directly.

Sample size: We will attempt to interview twenty children and their parents (all those receiving hydrotherapy). We will attempt to interview at least one interventionist and one research physiotherapist from each of the participating study centres.

Non-participation: Records of and spontaneously offered reasons for non-participation will be recorded and reported.

6.3 DATA COLLECTION

Timing: Semi-structured interviews will take place in the second year of the grant, after the last scheduled hydrotherapy session and research follow-up.

Setting: For their comfort, children and their parents will be interviewed in their own home, in person or by Skype. Interviews will be conducted in quiet and private settings to reduce distractions.

Interventionists may choose to conduct interviews face-to-face at the site closure visit or by telephone the same time.

Presence of non-participants. Parents / carers of participants will be present. Interventionists will be interviewed in isolation.

Description of sample. Demographic data on participants and their carers will be recorded.

Demographic and professional information on interventionists will be recorded.

Interview guides: Semi-structured interview contain questions about the acceptability of intervention and research protocols and have been piloted with interventionist and patient/carer members of the management group.

Repeat interviews: No repeat interviews will be undertaken.

Recording: All interviews will be recorded on encrypted digital recorders and fully transcribed. **Field notes:** will be taken during and after interviews as required.

Duration: Interviews are expected to average between thirty and forty minutes, with durations typically related to the age and capability of the child (Mahon et al. 1996). The researcher's sensitivity and judgement will be used to determine the length of the interview.

Data saturation:

Even allowing for the heterogeneity of the patient group, 20 interviews should be adequate to understand common perceptions and experiences of children receiving hydrotherapy, thereby achieving thematic saturation (Guest 2006) (as distinct from other forms of saturation (O'Reilly & Parker 2012)) on both intervention and study procedures. The concept of saturation will only be used to comment on the homogeneity of participant responses and will not affect the course of analysis, with all available transcripts analysed. Formal assessment of whether saturation has occurred or stopping criteria for qualitative data collection will not be employed (Francis et al. 2010). We do not anticipate data saturation in the interventionist interviews due to the small sample size.

Transcripts returned: Transcripts will not be returned to participants for correction.

6.4 ANALYSIS

Methodological orientation and theory:

General approach to qualitative research

Our approach is characterised by a subtle realism, interpretivism and pragmatism: we understand our subject matter through participants' contextually-situated perspectives; we strive for neutrality and objectivity during data collection and analysis; we attempt to be as transparent as possible as we move beyond the data during interpretation to serve the needs of policy-makers, health care practitioners and, most importantly, patients (Snape & Spencer 2003).

Theoretical approach to acceptability of research and intervention to participants

Previous qualitative research on the acceptability of physical therapy in children with neuro-muscular conditions mainly consists of inductive thematic analyses (Capjon & Bjørk 2010; Wiart et al. 2010; Christy et al. 2010). Only one study resorted to previously published models / theories of patient experience or behaviour to categorise participant views (Redmond & Parrish. 2008). The first is the Social Model Theory (SMT) of disability, which distinguishes impairment from disability (Tregaskis. 2002; Morris. 2001.) (defined as "disabling barriers of unequal access and negative attitude") and advocates policy changes, that eliminate discrimination and remove barriers of access to services. The other is the Theory of Psychosocial Development (TPD) (Erikson. 1968) which understands adolescence as marked by changes that require adaptations which can affect activities such as adherence to therapy and adaptation to illness. Both theoretical frameworks are likely to provide useful insights for both the design of the topic guide and the interpretation of the data set, but we do not consider either comprehensive enough. SMT has its detractors (Shakespeare et al. 2002). and there are numerous models which, unlike Erikson's, are specifically designed to understand intervention adherence, although none of them also incorporate the parent-child dynamic, as does

the TPD (Horne et al. 2005). It is because of the theoretical complexity of the clinical and commissioning decision problem under evaluation, as well as our preference for a pragmatic approach that we will employ Framework analysis. Framework analysis was developed by the National Centre for Social Research to address applied policy questions (Ritchie & Spencer 1994). Unlike some other qualitative methods, Framework analysis allows themes identified in advance to be specified from the outset (see derivation of themes) and for these to be combined themes that emerge by subjecting the data to inductive analysis. Framework analysis' great strength is that it allows ideas to be reformulated as the analytical process progresses. Protection against the researcher's own views, conflicts and prejudices are minimised by involving other researchers with different professional backgrounds (DH, ES and the study manager) and a patient representative in the analysis.

Theoretical approach to acceptability of research and interventions to interventionists

We will use Normalisation Process Theory as a framework to understand the conditions necessary to support the introduction and embedding of protocolised hydrotherapy as a routine element of care and to support the implementation of a trial for its evaluation (May & Finch 2009; Finch et al. 2013; Murray et al. 2010).

Number of data coders. DH and at one other researcher (either ES or CM) will independently blind code a sample of the transcripts, before conferring with each other and the study patient representatives to confirm the working coding tree. We will actively seek 'deviant' or 'negative' cases and modify emerging themes accordingly. The same two researchers will code all transcripts.

Description of the coding tree: will be available in the report.

Derivation of themes:

A handful of qualitative research studies have already investigated the views of patients and families on the acceptability of physical therapy programmes for young people with neurological conditions. The main themes related to: (a) improvement in physical function; Christy et al. 2010; Capjon & Bjørk. 2010; Wiart et al. 2010. (b) improvement in confidence and independence; Christy et al. 2010; Capjon & Bjørk. 2010; Wiart et al. 2010. (c) increased social participation; Christy et al. 2010; Capjon & Bjørk. 2010; Wiart et al. 2010. (d) achievement of goals; Christy et al. 2010; Capjon & Bjørk. 2010; Wiart et al. 2010. (e) fatigue during the programme; Christy et al. 2010; Capjon & Bjørk. 2010. (f) pain during the programme; Capjon & Bjørk. 2010 (g) the duration and spacing of therapy sessions; Christy et al. 2010. (h) the quality of the relationship with the therapist and communication between therapist and families; Capjon & Bjørk. 2010; Redmond & Parrish. 2008. (i) Stress associated with the programme and balancing therapy with the demands of everyday life; Christy et al. 2010; Wiart et al. 2010. (j) responsiveness of schools to children's therapy schedule; Capjon & Bjørk. 2010. Themes of a priori interest relating to the acceptability of the research protocol will be based on similar Sheffield CTRU topic guides on the subject and will include participant and health professional views on: being approached for participation at a difficult time; randomisation; the burden of research procedures, especially the battery of outcome assessments; and, which outcome assessments participants feel best reflect their concerns. Subthemes within umbrella categories will be derived inductively from reading the transcripts.

Software: Analysis of participant themes will take place in the latest version of NVivo (QSR International). With an anticipated small number of interventionists being interviewed, transcripts may be hand-coded.

Participant checking: Participants will not provide feedback on the findings.

Quotations: will be presented, without identifiers beyond 'participant', 'parent/guardian', or physiotherapist, to illustrate the themes.

7.0 TREATMENT FIDELITY SUB STUDY

One aspect of this feasibility study will be to assess the consistency of the hydrotherapy and land-based interventions across centres and therapists. The process is complex as there is (a) a need to optimise treatment based on the participant's level of ability; (b) a requirement for independent review of treatment schedules submitted by participating physiotherapists to assess whether they were optimised by the participant's ability. A fidelity-assessment / quality assurance exercise is planned to take place using the data we propose to collect in section 5.4 above.

8.0 DATA COLLECTION

The CTRU will co-ordinate follow-up and data collection in collaboration with the research sites. Data will be collected either on study specific CRFs or where possible, directly onto a remote web-based data capture system. Data will all be transferred to the CTRU for analysis. Members of the study team at the research sites will be responsible for cleaning the data provided locally as queries are raised remotely in data collection system. Details of data collection forms and items are listed in table 3 below:

Table 3: Data collection

		Where	Completed by	Format		Consent and screen (visit 1)	Eligibility and baseline (visit 2)	Intervention	26 weeks (visit 3)
FORMS and OUTCOME MEASURES				Paper	Electronic				
<i>Informed consent</i>		Clinic	Participant/carer	x		x			
<i>Eligibility criteria form including:</i>				x		x	x		
NSAA		Clinic	Physio	x	x	x	x		x
6 minute walk test		Site/clinic	Physio				x		x
FVC		Clinic	Physio	x	x	x	x		x
<i>Patient reported outcomes</i>									
Child health Utility 9D		Clinic or home	Participant	x			x		x
ACTIVLIM		Clinic or home	Participant	x			x		x
Carer QoL		Clinic or home	Carer	x			x		x
Health and social care resource use		Clinic or home	Participant/carer	x			x		x
	Pain (VAS)	Clinic or home	Participant/carer	x				x	
	OMNI scale of perceived exertion	Clinic or home	Participant/carer	x				x	
Concomitant medications		Clinic or home	Physio		x	x		x	x
Adverse and Serious adverse events		Clinic, home, other	Participant/carer/physio		x			x	x
<i>Intervention and fidelity assessment</i>									
Manualised hydrotherapy proforma		Pool, Clinic	physio	x				x	x
Manualised LBT proforma		Clinic, Home	Participant/carer/physio	x				x	x
Participants views on intervention and research procedures		Home, CTRU	Participant/researcher	x				x	
Therapists views on intervention/ research protocol		Clinic, CTRU	Physio/researcher	x				x	
Care plan prescribed for intervention and control		Clinic, pool	Physio	x				x	
<i>Feasibility outcomes</i>									
Number and characteristics of eligible patients approached: <i>screening form</i>		Clinic	Physio	x	x	x			
Reasons for refused consent: <i>screening form</i>		Clinic	Physio	x	x	x			
Reasons for attrition: <i>withdrawal form</i>		Clinic, home	Physio					x	x
Participant attrition rate:		CTRU	Researcher		x			x	x
Number of missing values/incomplete cases		CTRU	Researcher	x				x	x
Feasibility of recruiting participating centres:		CTRU	Researcher						
Participants and therapists views on acceptability		Research site, home	Participant/researcher					x	

Data will either be collected directly from the participants, carers or physiotherapists or from source documents (e.g. patient notes) and input onto the CRF or electronic web based system. The Data Monitoring and Management Plan for the study will provide further guidance on the types and levels of data and how these will be monitored and verified. Table 3 above details the format, the time points when the data are collected, by whom and where.

9.0 DATA HANDLING AND RECORD KEEPING

The research staff at sites (research nurse or physiotherapists) will be responsible for data entry locally. Sheffield CTRU Trial Manager, research assistant and the Data Management Team will work with sites to ensure the quality of data provided. Data will be collected and retained in accordance with the Data Protection Act 1998. Anonymised trial data will be entered onto a validated database system designed to an agreed specification between the Chief Investigator and Sheffield CTRU. The study manager, research assistant, data manager, PI's, research nurses and physiotherapists will have access to the anonymised data on the database through the use of usernames and encrypted passwords. The system has a full electronic audit trail and will be regularly backed up. The secure data management system will incorporate quality control procedures to validate the study data. Error reports will be generated where data clarification is needed. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Chief Investigator. Trial documents will be retained in a secure location during and after the trial has finished.

The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of participant data. Prospect stores all data in a PostgreSQL database on virtual servers hosted by Corporate Information and Computing Services (CiCS) at the University of Sheffield. Prospect uses industry standard techniques to provide security, including password authentication and encryption using SSL/TLS. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This can be used to restrict access to personal identifiable data.

Participants who give consent to the qualitative part of this study will also give consent to their name and address to be given to the University of Sheffield qualitative research staff in order to be contactable. Participant confidentiality will be respected at all times. Participant names and contact details will be collected and entered on the database. Access to these personal details will be restricted to users with appropriate privileges only. All users who do not require access to identifiable data will only identify data by participant ID number, and no patient identifiable data will be transferred from the database to the statistician.

Trial documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All source documents will be retained for a period of 5 years following the end of the trial. Where trial related information is documented in the medical records – those records will be retained for 5 years after the last patient last visit. Each site is responsible for ensuring records are archived and the information supplied to the Chief Investigator.

10.0 ACCESS TO SOURCE DATA

The sponsor will permit monitoring and audits by the relevant authorities, including the Research Ethics Committee. The investigator will also allow monitoring and audits by these bodies and the sponsor, and they will provide direct access to source data and documents.

11.0 STATISTICAL ANALYSIS

Sample Size

This study is an external pilot trial intended to explore the feasibility of conducting a future definitive trial and to estimate important parameters to inform its design. The sample size is based on the need to estimate study parameters within a reasonable degree of precision rather than on hypothesis testing. After simulation work, Browne recommended a minimum of 30 participants (15 per group) in order to achieve pilot/feasibility objectives involving parameter estimation (Browne, 1995). Current 'rules of thumb' suggest sample sizes of between 12 and 30 per group are necessary to estimate the key parameter associated with a continuous outcome, namely the standard deviation (SD) with a reasonable degree of precision (Julious, 2005; Sim, 2012). Assuming a dropout rate at six months of 20%, we will need to consent and randomise at least 40 participants (20 per group).

Data Analysis

As the study is a pilot randomised control trial, data will be reported and presented according to the proposed modifications for reporting pilot trials as well as the CONSORT statement (Thabane, 2010; Kenneth, 2010). The statistical analysis will be performed on an intention-to-treat basis. We will present descriptive statistics for feasibility and clinical outcomes by group, study visit and overall (significance testing will not be undertaken). Continuous outcome measures will be presented as mean differences between groups and their associated 95% confidence intervals whilst for the categorical outcomes the percentages falling into different categories and potential differences between groups in terms of the percentages in each category will be presented, together with their confidence intervals. These results will then be used to estimate the sample size for a definitive clinical trial considering a range of outcome measures and assumptions to determine whether a clinically meaningful trial can be conducted within a satisfactory timescale and cost envelope using UK centres alone. A detailed analysis plan will be prepared to specify all a priori analyses.

The Sheffield CTRU will oversee randomisation, undertake data management and analysis and ensure the trial is undertaken according to Good Clinical Practice Guidelines and CTRU standard operating procedures. The analysis will be performed after data lock by a CTRU statistician under the supervision of the senior study statistician.

12.0 ECONOMIC EVALUATION

The pilot study will identify the main drivers of i) the NHS and social care cost and ii) societal costs (including carer time) in patients with DMD, namely GP visits, treatments, investigations, and investigations. Costs will include the delivery of the intervention, including the time taken to deliver the service, staff type, staff to patient ratios, overheads and fixed costs. This study will not have a definitive answer on the cost-effectiveness of the intervention being considered, but rather will help explore the resource use and the feasibility of collecting resource use and quality of life information from patients with DMD.

Costs

Resource use will be captured through patient-level surveys plus information recorded routinely in patient record. Unit cost information will be taken from standard resources and will include unit costs from NHS reference costs (Department of Health,2013), the personal social services research unit (PSSRU) (Curtis, 2013), the British National Formulary (<http://bnf.org/bnf/index.htm>) and the Office of National Statistics, Annual Survey for Hours and Earnings (Office of National Statistics, 2013). This information will be used to produce cost for each patient within the pilot trial.

Quality of life

Health related quality of life will be measured using the Child Health Utility (CHU) 9D a utility measure developed and tested in children aged 7 to 17 years (Stevens, 2009; Stevens 2012). The CHU-9D will be used to generate quality adjusted life years (QALYs). The appropriateness and sensitivity of the measure will be established in the pilot study.

Cost-effectiveness analysis

As it is a pilot trial, this study will not have a definitive answer on the cost-effectiveness of hydrotherapy in patients with DMD, but rather will help to explore the resource use. We will follow established methods in statistical analysis of this data to reflect uncertainties in the estimates and to identify which parameters are important drivers of the incremental cost effectiveness ratio (ICER). Drawing on these costs, and by estimating the likely costs of the service we will undertake Expected Value of Perfect Information (EVPI) analysis, which will be used to determine the feasibility of hydrotherapy in the pilot trial. The main outcomes of the cost-effectiveness models will be the cost per quality adjusted life year (QALY).

13.0 SAFETY ASSESSMENTS

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Definition

An SAEs or SARs is an event that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- is another important medical event that may jeopardise the subject***

* 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any serious adverse events or adverse reactions which a member of the study team (e.g. research nurse, research physiotherapist) deems to be associated with the trial intervention

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Definition

SUSARs fulfil the criteria for SAEs listed above but in addition to this are classified as also both “UNEXPECTED” and “RELATED” to the trial intervention; these may be reported for an event in the control group.

Any serious adverse events that meet the criteria above will be reported on an adverse event form on the case report form and database. Those that qualify for meeting the category of SUSAR will be **reported by the site to both the Clinical Trials Unit and to the Sponsor within 24 hours of their discovery** at site. Expedited reporting will be conducted by the sponsor (or their delegate) to the research ethics committee within the timeframes specified by the Health Research Authority.

A member of the site study team will enquire about any adverse events since the previous visit and record these on the adverse event paper CRF and database. For any Serious Adverse Events an SAE paper CRF and database entry will be completed. The event will be assessed by the local Principal Investigator and the form will be kept in the site file. Serious adverse events will be reported in the periodic safety reports to the research ethics committee and the Trial Steering committee.

Expected adverse events

The following adverse events are expected within the trial and will be reported in the “Expected adverse events” section of the case report form:

- 1) Falls
- 2) Delayed muscle onset soreness
- 3) Chest infections
- 4) Symptoms of sleep hypoventilation
- 5) Flu/pneumothorax immunisations

Adverse event inclusions

Data will be collected in relation to the following three specific adverse events from children in the intervention group **following every hydrotherapy session** on the case report form.

1. Pain (visual analogue scale)
2. Children's OMNI Scale of Perceived Exertion

Other key adverse events which participants and sites will be asked to report throughout the trial include:

1. Pain
2. Fractures
3. Acute infections

Adverse events will be recorded in accordance with CTRU Pharmacovigilance Standard Operating Procedures.

All adverse events (serious or other based on the definitions above) will be recorded on the case report form and details will be updated on the web based system **within 1 week of completing the paper form**. If an adverse event fulfils the criteria for being a SUSAR (see definition above) the SAE form will be completed by a member of the team at the site and a copy will be faxed both to the Trial Manager (at CTRU) and to the Sponsor **within 24 hours of discovery**. The CTRU, Sponsor and CI will liaise and check if any additional details are required from the site after which the SUSAR will be reported to the REC within the required timeframe.

Monitoring

The study will be registered with the local R&D department of each centre and Sheffield Children's Hospitals Trust will act as the sponsor for the Trial. Two committees will be established to govern the conduct of this study: the Trial Steering Committee (TSC) and a Trial Management Group (TMG). These committees will function in accordance with Sheffield CTRU standard operating procedures. The TSC will consist of a neutral chair with clinical and research expertise in paediatrics, an independent statistician, a physiotherapist with research experience, and up to two patient representatives. The Committee will meet approximately every 6 months from the start of the trial. The Trial Manager will be jointly supervised by the CI and the Assistant Director of the Sheffield CTRU and will liaise with the whole study team. Trial monitoring procedures and site monitoring will be undertaken at a level appropriate to a risk assessment performed by the sponsor or their delegate and in accordance with CTRU SOPs.

The trial will be conducted subject to Research Ethics Committee favourable opinion including any provisions for site specific assessment. The application will be submitted through the IRAS central allocation system. The approval letter from the ethics committee and copy of approved patient information leaflet, consent forms and any ethically approved questionnaires will be present in the site files before initiation of the study and patient recruitment. Local research governance approvals will be sought from all participating research sites.

This clinical trial will be conducted in accordance with Good Clinical Practice Guidelines and CTRU standard operating procedures.

14.0 FINANCE AND INDEMNITY

The trial has been financed by the HTA and details have been drawn up in a separate agreement. This is an NHS sponsored study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity will cover NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

15.0 REPORTING AND DISSEMINATION

As this is a feasibility study its main interest will be to potential researchers and funding bodies. Data will be reported according to the revised CONSORT statement (Schultz, 2010). The findings of this research will be available to NIHR, patient groups and other interested bodies. It will also be offered for presentation at medical meetings and will be offered for publication in peer reviewed medical journals. Prior to the study a consensus statement will be agreed for both optimal land based therapy and for hydrotherapy for people with DMD in the UK, allowing for budget and access constraints, which will be freely available and offered to patients groups such as the MDC.

The HydroDMD trial is funded by the National Institute for Health Research's Health Technology Assessment Programme.

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