Lancashire Teaching Hospitals

NHS Foundation Trust

CENTRE FOR HEALTH RESEARCH AND INNOVATION

Protocol – version 3, 22 August 2023

Title:
Hydrotherapy for health in boys and adolescents with Duchenne muscular dystrophy

Short Title:
Hydrotherapy in DMD

Study Team & Collaborations:

Chief investigator: Dr Christian De Goede, Consultant Paediatric Neurologist, Lancashire Teaching Hospitals NHS Trust. Christian is a consultant paediatric neurologist with a keen interest in research, working closely with local universities. He is the lead for paediatric neuromuscular service in Lancashire and South Cumbria. He has worked on a number of collaborations with MMU, looking at activity and pain in children and adults with muscular dystrophy. Christian will lead the clinical side of the project with his team as a principal investigator.

Co-Investigator: Dr Christopher Morse, Reader in Exercise Physiology, Department of Sports and Exercise Sciences, Manchester Metropolitan University. Christopher is a Reader in Exercise Physiology based at MMU Cheshire. His research looks at how neuromuscular function is affected by old age, lifelong conditions and physical activity. He has collaborated with the Neuromuscular Centre to undertake research in exercise, physiotherapy, diet and physical activity in adults with muscular dystrophy. Chris will be the academic lead for the study.

Dr Petra Kolić, Senior Lecturer in Sports Coaching. Petra is a qualitative researcher investigating sociological aspects of health and wellbeing related to physical activity. Petra will conduct and analyse the qualitative interviews drawing upon 100s of hours of interview experience from her previous studies.

Paula Sugden, Paediatric Research Nurse, Lancashire Teaching Hospitals NHS Trust. Paula works as a research nurse in the Child Health Department at Royal Preston Hospital. She has a wide role in the set up and management of research studies in children, and advocating research in our trust. She has been closely involved in the development and running of a trial looking at a new device to help children who wet the bed, and is about to start an exciting study looking at determinants of activity in children with muscle conditions. Supporting the clinical physiotherapist, Paula will be involved in the set up recruitment and management of the study.

Natalie Mattos-Harris, Paediatric Research Nurse, Lancashire Teaching Hospitals NHS Trust. Natalie is a nurse in Child Health Department at Royal Preston Hospital. She is a research nurse, and also works as a neonatal nurse on the level 3 neonatal unit. She has been involved with a number of studies in children and neonates. Together with Paula, Natalie is about to start an exciting study looking at determinants of activity in children with muscle conditions. Supporting the clinical physiotherapist, Natalie will be involved in the set up recruitment and management of the study.

Dr Kina Bennett, Research Operations Manager, Lancashire Teaching Hospitals NHS Trust. Kina represents the LTHTR trust as the sponsor for this study.

Background *(Literature review):*

There is a doubling of body fat (BF%) in young males with Duchenne Muscular Dystrophy (DMD) (Mayo et al., 2012), which may represent a significant contributory factor to co-morbidities associated with this untreatable neuromuscular condition. In adults with DMD and BMD we have found that, a higher BF% is associated with impaired glucose tolerance (Bostock et al., 2018) and lower perceived quality of life (QoL, Jacques, Stockley, Onambele-Pearson, et al., 2019). Similarly, boys and adolescents with DMD have lower perceived QoL (Kohler et al., 2005), and can show evidence of mental health issues (Steele et al., 2008) commonly associated with progressive disability. This progressive physical impairment, coupled with high levels of bodily pain (Hunt et al., 2016), likely contributes to boys and adolescents with DMD having lower daily physical activity levels and subsequently higher BF% and BMI than age matched boys without DMD (McDonald et al., 2005). Furthermore, an accumulating BF% in boys and adolescents with DMD may accentuate functional impairments such as lower limb weakness, as anti-gravity muscles are having to overcome an increasing body mass.

Within boys with DMD, hydrotherapy is recommended (Bushby et al., 2005), yet in contrast to other neuromuscular conditions, within DMD there is scant evidence that hydrotherapy benefits QoL, pain and mobility. These quantifiable outcome measures have all shown benefit from longitudinal hydrotherapy in other populations including fybromyalgia, osteoarthritis, stroke and spinal muscle atrophy (Karjalainen et al., 1999; de Mattos et al., 2016; Marinho-Buzelli et al., 2014). Within DMD, data is limited to small participant numbers, with some benefit of hydrotherapy shown in 1, 6 or 8 boys, compared to 2-6 boys not receiving the treatment (Honório et al., 2013; Honório, 2011; Hind et al., 2017). Where smaller groups of data are presented e.g., 8 boys with DMD receiving hydrotherapy, the focus was on 6-minute walk distance, rather than QoL or pain, and was again limited to comparisons with 2 control participants (Hind et al., 2017). In contrast, within Spinal muscle atrophy, improvements in QoL have been reported with frequent hydrotherapy (Cunha et al., 1996).

Despite evidence that low intensity exercise may benefit, or at least not negatively impact, physical function and daily pain in DMD (Hunt et al., 2016; Jansen et al., 2013), there is at present a lack of evidence to suggest that those with DMD should undertake hydrotherapy, despite favourable anecdote (MDUK, 2015) and case reports. Previously, we have identified a modest metabolic response following low intensity hand cycling in non-ambulatory men with DMD (Morse et al., 2018). This cardiorespiratory impact was however, limited to those with the most functional upper limbs. Specifically, of those completing the study 2 men aged 18 and 20 were able to increase their metabolic rate to a level that would induce a meaningful health benefit. It could be hypothesized therefore, that young males (aged 6-18) with DMD have the potential to induce health benefits from active hydrotherapy movements. In contrast, those with limited mobility or active musculature, may experience benefits from passive hydrotherapy (e.g. pain and joint mobility). An exercise diary will be recorded for every hydrotherapy session, and with a sufficient sample of 20 participants, it will be possible to analyse the results of the study as a single intervention group with exercise intensity as a covariable to outcome adaptation, consistent with our previous sedentary behaviour interventions in other populations (Ryan et al.,

2018). This project therefore seeks to: 1) undertake a hydrotherapy intervention in boys and adolescents with DMD and 2) conduct qualitative Patient and Parent interviews to understand the potential barriers and hidden benefits to hydrotherapy not captured in our outcome measures.

Research Objective:

It is hypothesised that undertaking hydrotherapy will result in a beneficial change in the primary outcomes of QoL, bodily pain, and body composition, and secondary outcomes of physical function (e.g. Range of motion strength, and upper limb function), where possible.

The **aim** of this study is to determine whether hydrotherapy can mitigate some of the weight gain, bodily pain, lower QoL and functional impairments associated with progression of DMD in young males.

Potential outcomes include:

1) improvements in all outcome measures as a result of undertaking hydrotherapy (increased lean muscle mass, reduced body fat; improved functional measures (e.g. strength), activities of daily living, ROM; improved quality of life, and lowered bodily pain).

2) no change in outcome measures-following hydrotherapy but a relative slowing of the decline observed during the "control period".

3) outcome measures continue to deteriorate at the same rate as the control period.

4) a worsening of outcome measures compared to the control period.

Objectives and Specific Aims:

Outcomes

This project will yield 4 experimental journal articles.

1. The impact of hydrotherapy on body composition and muscle mass in boys with DMD
2. The impact of hydrotherapy on QoL and bodily pain in boys with DMD
3. The impact of hydrotherapy on muscle function and activities of daily living in boys with DMD
4. Practical considerations and barriers to hydrotherapy in young people with DMD, a qualitative review of interviews with parents, carers and those with DMD.

As the first hydrotherapy study within DMD, the overarching outcome will be to determine whether it is efficacious and beneficial to complete a longitudinal hydrotherapy intervention in young males with DMD, which will inform future guidelines on activity within this population. To this end we will conduct qualitative interviews and work alongside the members of the Northwest Neuromuscular network, and the Neuromuscular Centre (Winsford, UK) who regularly undertake hydrotherapy to engage with service users with DMD to provide guidelines for physical activity based on our previous work on sedentary behaviour (Jacques et al., 2018) and the findings of this proposed project.

Qualitative interviews

Face-to-face interviews will be conducted with 20 participants from the study. This will include a mixture of those with DMD, and their parents, to understand what barriers are faced when undertaking hydrotherapy, what about the hydrotherapy intervention was suitable, and whether there are benefits to hydrotherapy not captured in our outcome measures (Bagley et al., 2016). The interviews will be approached from an interpretivist perspective to make sense of the lived

experiences of those involved in the hydrotherapy (Schwartz-Shea and Yanow, 2013), consistent with the expertise within our research team. In addition to a scientific publication, these qualitative findings will inform the development of future guidelines on hydrotherapy and allow us to optimise participant benefit through relevant research.

Rationale and Significance of Study:
Protocol design justification

While natural history studies indicate an overall negative trend in the abilities of patients with DMD, there is great variability in age and speed of deterioration (Muntoni et al., 2019). As such it is difficult to find matched controls for a short randomised intervention study. Instead, due to the progressive nature of DMD and the inherent variance within a mixed age, and ability population (e.g. upper limb & respiratory function, genetic variation etc.(Ricotti et al., 2019)), the participants will act as their own controls. This single-arm, non-crossover design where the participant acts as his own control, although not as robust as randomized control exercise trials, is advocated for longitudinal interventions in populations such as the present one (Hecksteden et al., 2018). Indeed, this self-controlled approach offers some of the benefits of prospective controlled trials, allows for multiple treatments within the same participants, and eliminates some of the covariates of group comparisons which are inherent in dual arm training studies (Vohra et al., 2015). Specifically with treatments such as hydrotherapy, the process of randomisation leads to patient and parent disengagement due to not getting to undertake a treatment (Hind et al., 2017). This self-controlled study avoids the downsides of randomisation for the participants and is consistent with previous exercise training studies both in non-clinical (Narici et al., 1989), and in our own training studies in muscular dystrophy (Bostock et al., 2019).

Research Design

The **aim** of this project is to undertake 12-weeks of hydrotherapy in boys and adolescents with DMD, and monitor the impact on body composition, bodily pain, QoL and physical function. The project is broken down into 3 key stages:

Pre-experimental stage: during this stage we will secure ethical approval, and recruit participants. This stage will last ~6 months due to the length of time it takes to secure NHS ethical approval.

Experimental stage: the participants will complete the experimental protocol described below in detail. Briefly, participants will complete TWO 12-week periods. The first will be an observation (control) period to use as a reference point for the second period, which will involve 12-weeks of hydrotherapy. *Figure 1* attached describes the testing sessions; these will be completed at 3 time points, the first before the control period, the second after the control period, and the third after the hydrotherapy period. The experimental stage will last 28-months due to the staggered recruitment and testing of participants.

Post experimental stage: this stage will involve the analysis of data and production of academic papers for submission within international journals. This stage will be scheduled for 4-months but will continue until the data has been published. Although the cost of a dissemination event is not formally included within this bid; as researchers and clinicians we regularly update physiotherapists, carers, clinicians and those with DMD through dissemination events. We plan to present our findings at events hosted through the

Northwest Neuromuscular Network, The Neuromuscular Centre outreach and dissemination days, and through the hospice website.

Experimental stage protocol

Participants will complete two 12-week periods, including an initial control period (CTRL), where they will undertake their habitual physical activity behaviour. This will be followed by 12-weeks of hydrotherapy, where participants will complete up to 60 mins of hydrotherapy once a week. During these CTRL and hydrotherapy periods, diet and physical activity will be monitored to identify any lifestyle covariates that could contribute to their body composition and physical and mental wellbeing. Pre and Post CTRL, and Post hydrotherapy, participant outcome measures will be re-assessed.

Consent: consent will be obtained from patients 16 years and older or parents / guardians of children younger then 16 years of age, either face to face or via a pre-arranged video link with a member of the research team who is signed off the delegation log as being able to take consent.

If consent is taking place face to face, a suitable time will be arranged between a member of the research team and the family. Consent can take place during the patient's usual Neuromuscular clinic or at an independent appointment at the Clinical Research Facility (CRF). This is also a good opportunity for the young person to familiarise themselves with the CRF.

If consent is taking place via a pre-arranged video link, a suitable time will be arranged between patient/parents/guardians and a member of the research team. Microsoft Teams, Attend Anywhere or Zoom are acceptable platforms that can be used depending on individual Trust guidelines. A copy of the PIS and the appropriate consent form (with all details completed by Research Team as needed) will be posted to the family with a pre-paid return envelope.

During the consent appointment, either face to face or via video link:

1. A member of the research team will confirm they have received the PIS, have read it and have understood it.

2. Patient/ Parents / guardians will be asked if they have any questions.

3. Questions will be answered until they are content.

4. The research team member taking consent will re-confirm the fact that the child can be withdrawn at any time without giving any reasons and that this will not affect the physiotherapy treatment the child receives.

5. The patient/parents/guardians will then be given the consent forms. They will be asked to read every statement, initial each box, and sign and date at the end of the form.

6. The research team member taking consent will then sign and date the form. If appointment is completed via video link, the wet ink copy is posted back to the research team to sign and date and note that the form was completed by parents during the video link.

7. The wet ink copy will be kept by the research team member.

8. A copy of the signed consent will be given to the patient/ parents / guardian to keep for their own records. If via video link, this copy will be posted to parents or given when the family attend for their initial assessment.

Participants and power calculation

We are adopting an inclusive approach to participant recruitment, which is possible through the within group design of the control and hydrotherapy interventions. To this end, we aim to recruit 44 male participants aged over 6 years of age, who have previously been diagnosed with DMD from multiple neuromuscular centres in the Northwest Neuromuscular Network (Royal Preston, Manchester, Alder Hey, Oswestry) and from Derian House Children's Hospice (Chorley, UK). Participants will be included if they are able to undertake a single bout of hydrotherapy lasting at least 45 minutes, and are not currently ventilated during the day. An initial assessment will be performed by the clinical physiotherapist associated with the project (See attached *Figure 2*-Gant Chart). Exclusion criteria will include any regular hydrotherapy exercise within the preceding 12 weeks.

There are at present limited data on the effect of hydrotherapy on QoL in DMD from which to base a power analysis, therefore we have carried out our analysis using a previous hydrotherapy intervention in adults with Osteoarthritis (Fransen et al., 2007). It should be noted that their pre intervention QoL scores were similar to those we have collected in DMD participants [DMD = 34.3(5.9), Osteoarthritis = 31.9 (8.5), (Means(SD))].

Within their 24 sessions of hydrotherapy, Fransen et al (2007) report effect sizes above that of control of 4.0, with no change in their control group. If we make the assumption that within our 12 session intervention we are likely to see half of the improvement in QoL, we shall base our power analysis of an effect size of 2 compared to that of controls. With the following values, within participant *apriori* power calculation performed using G*Power (Version 3.1.7, University of Kiel, Germany) suggests a total group number of n = 8 (α err prob=0.05, Power 0.95). We feel this is too conservative given that we also need to a) account for drop-out of participants and b) fulfil the criteria for paramatricity in a clinical condition that has a wide variance (children and adults with DMD ranging from 6-25 yrs are vary varied in the presentation of physical function). Therefore, given the aforementioned considerations and as this is a novel intervention in terms of research outcomes and will serve as a primary point of reference for subsequent hydrotherapy studies within DMD, we will recruit 44 participants in total.(See also *table 1*, summarising published hydrotherapy trials in similar medical conditions)

Participants will be recruited through the respective neuromuscular clinic and through Derian House hospice.

Inclusion criteria

- Established diagnosis of Duchenne Muscular Dystrophy (either by genetics or muscle biopsy)
- Between 6 and 25 years of age
- On stable dose of steroids or not on steroids

Exclusion criteria

- Younger than 6 years, older than 25 years
- Recent change in steroid dose, less than 3 months prior
- Undertaking formal hydrotherapy supervised by physiotherapist on a regular basis (weekly or more frequent)

Body composition

Fat mass, body fat percentage and fat free mass will be measured using bioelectrical impedance (BIA). Although more stringent measures of body composition exist such as dual-energy X-ray absorptiometry (DEXA), BIA has been validated in DMD and is accurate enough to measure longitudinal changes in body composition and muscle mass in this population (Mok et al., 2010; Kuru et al., 2019).

Physical function

Established physical function assessments for individuals with neuromuscular conditions will be completed. These will include the North-Star and Performance of the Upper Limb assessment (Mayhew et al., 2013); and an assessment of activities of daily living (Wu et al., 2011).

Limited ankle range of motion (ROM) has long been recognised as a characteristic of children with DMD (Archibald and Vignos, 1959). Hydrotherapy has proven successful to offset impairments in children with ankle contractures albeit with Cerebral palsy (Kesiktas et al., 2004); ankle plantarflexion-dorsiflexion (PF-DF ROM) will be assessed through a goniometer.

Grip and pinch strength will also be assessed using digital, handheld dynamometers.

Pulmonary function

Participants will complete lung function measures using digital spirometry.

Mental wellbeing, QoL and pain

The PedsQL QoL questionnaire will be used to assess QoL, as it is a reliable measure of disease-specific health-related QoL in those with DMD from childhood to 18 yrs of age (Davis et al., 2010). In addition we will use the PedsQL multidimensional fatigue scale. We will also use the DMD-QoL and DMD-Qol Proxy, a recently developed tool to measure quality of life in patients with DMD. In addition, a pain map assessment of the topographic distribution of daily pain will also be competed, consistent with our previous work in DMD (Jacques, Stockley, Bostock, et al., 2019). We will also include a participation measure (CASP)

Physical activity and diet

Triaxial accelerometers will aim to be worn for up to 7-days during the first week of CTRL and hydrotherapy. We have previously adopted this approach in adults with MD, and have reported meaningful associations between habitual PA and both QoL and ADL (Jacques et al., 2018).

Over 7-days during both CTRL and hydrotherapy periods, participants will record daily food intake for 3 days using a smartphone app. Subsequent analysis will be performed using dietary analysis software (Nutritics).

Intervention

During the 12-week hydrotherapy intervention, participants will complete a weekly hydrotherapy session lasting from 30 to 60 mins. This is a duration and frequency of

hydrotherapy consistent with previous studies that have shown improvements in QoL in fibromyalgia (Mannerkorpi et al., 2002), physical function in Parkinson's disease and multiple sclerosis (Salem et al., 2011; Vivas et al., 2011), and functional independence and mental health in adolescents with cerebral palsy (Dorval et al., 1996). An overview of previous studies and hydrotherapy parameters is provided in Table 1.

The exercises, intensity and specific hydrotherapy session plan will be derived from consultation between the participants, and clinical physiotherapist. Due to the variance within the presentation of the condition and the inclusive age range within the study, we will take what we consider as an externally valid approach to exercise prescription. We will record heart rate during a sample of the participants' hydrotherapy sessions, which will be included as a co-variate for subsequent analysis.

Hydrotherapy will be conducted at Derian House Children's Hospice (Chorley, UK), and may include weight-bearing activities such as standing and gait practice, assisted and resisted limb exercises. Core and trunk work including swimming.

Please find attached

Figure 1-experimental overview
Figure 2-GANTT chart
Figure 3- proposed experimental workflow
Table 1 -current research in hydrotherapy

Data Analysis:
All participants will be assessed using a repeated measures design. Given the broad heterogeneity of DMD participants recruited there is no meaningful benefit of intergroup comparisons between those participants who can complete 30-60 mins of active hydrotherapy, compared to those who can perform arm only, or passive hydrotherapy. Experimentally it is not of interest if one group changes more than another, it is of interest if there is a change within the individuals themselves. We have recently completed a resistance training protocol in adults with MD and adopted a similar approach (Bostock et al., 2019).

Participants will be assessed against previous time points (Pre-CTRL vs Post-CTRL vs Post hydrotherapy) using repeated measures Anova (where outcomes are parametric) or Friedman's (where parametric assumptions are violated). Tests of association will be used to compare relative hydrotherapy intensity with changes from PRE to Post hydrotherapy.

Adverse Events:
All adverse events will be reported to the Chief Investigator and study Sponsor. Depending on the nature of the event the reporting procedures below will be followed. Any questions concerning adverse event reporting will be directed to the Chief Investigator in the first instance.

Adverse Events

If an incident needs acute attention, a member of the research team will follow local emergency procedures.
These will be recorded using the Adverse Event Reporting form, discussed with CI and paediatricians/ physiotherapist of team and escalated to the study Sponsor.

Serious Adverse Events

No SAE is anticipated, however, in the event of a suspected SAE occurring a form will be completed by a member of the research team, who will then notify (in person or via Egress secure email) the Chief Investigator and Sponsor representative within 24 hours. The Chief Investigator and Sponsor will assess and determine if the SAE is related to the study procedures and report back to the research team via e-mail.

All SAEs will be reported to the ethics committee where, in the opinion of the Chief Investigator, the event was: 1 'related', i.e. resulted from the administration of any of the research procedures; and 2 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence. Reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event, using the SAE form for non-IMP studies.

Monitoring:

The conduct and running of this research project will be overseen by the Chief Investigator which may be delegated to lead research physiotherapist. They will audit and monitor the research through all the stages and until completion on a risk assessed basis. The audit and monitoring process will be conducted in line with the terms of funding for the research and in line with LTHTR's policies, procedures, and the Research Governance Framework.

Local teams will also be answerable to their local R&D department, who will also monitor and audit all research undertaken at the Trust.

Dissemination:

The results of this study will be used to inform the neuromuscular service in Preston and at other sites in the UK. The results will also be shared more widely by presenting them at regional and or national meetings. The results may be published in a scientific journal and presented at scientific medical conferences and through publications and meetings organised by Duchenne UK. Outcomes will also be shared by DMD Care UK to help improve the standards of care. You will not be identified in any report or publication.

Ethical issues:

Ethical review and approval will be sought through an application through IRAS. (Reference 304633)

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Test	PRE CTRL	12 WK CTRL	Post CTRL	12 WK HYDRO	POST HYDRO
BMI (Kg/m^2)	✓		✓		✓
Body Fat%	✓		✓		✓
LMM (Kg)	✓		✓		✓
PUL	✓		✓		✓
NSTAR	✓		✓		✓
Grip	✓		✓		✓
NEADL	✓		✓		✓
Lung function	✓		✓		✓
PF/DF ROM	✓		✓		✓
Pain Maps	✓		✓		✓
SF36	✓		✓		✓
DMD QoL	✓		✓		✓
Peds-QoL	✓		✓		✓
7-Day PA		✓		✓	
3 Day Diet		✓		✓	
Qualitative interview					✓

Figure 1: Proposed outcome measures and assessment schedule

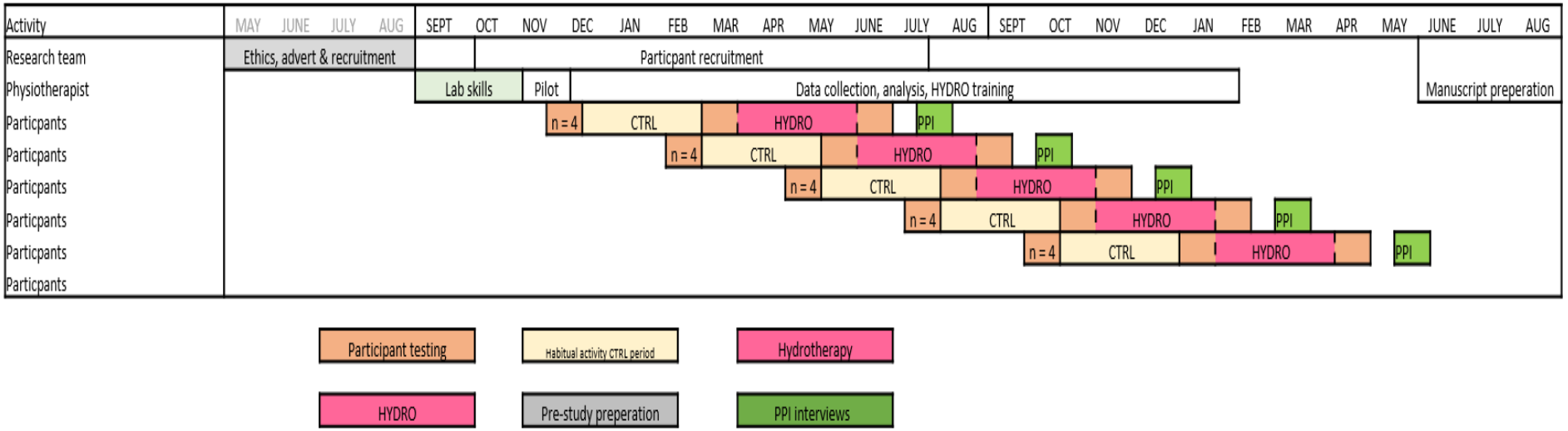

Figure 2: GANT chart showing the procedures over the 2 year study period.

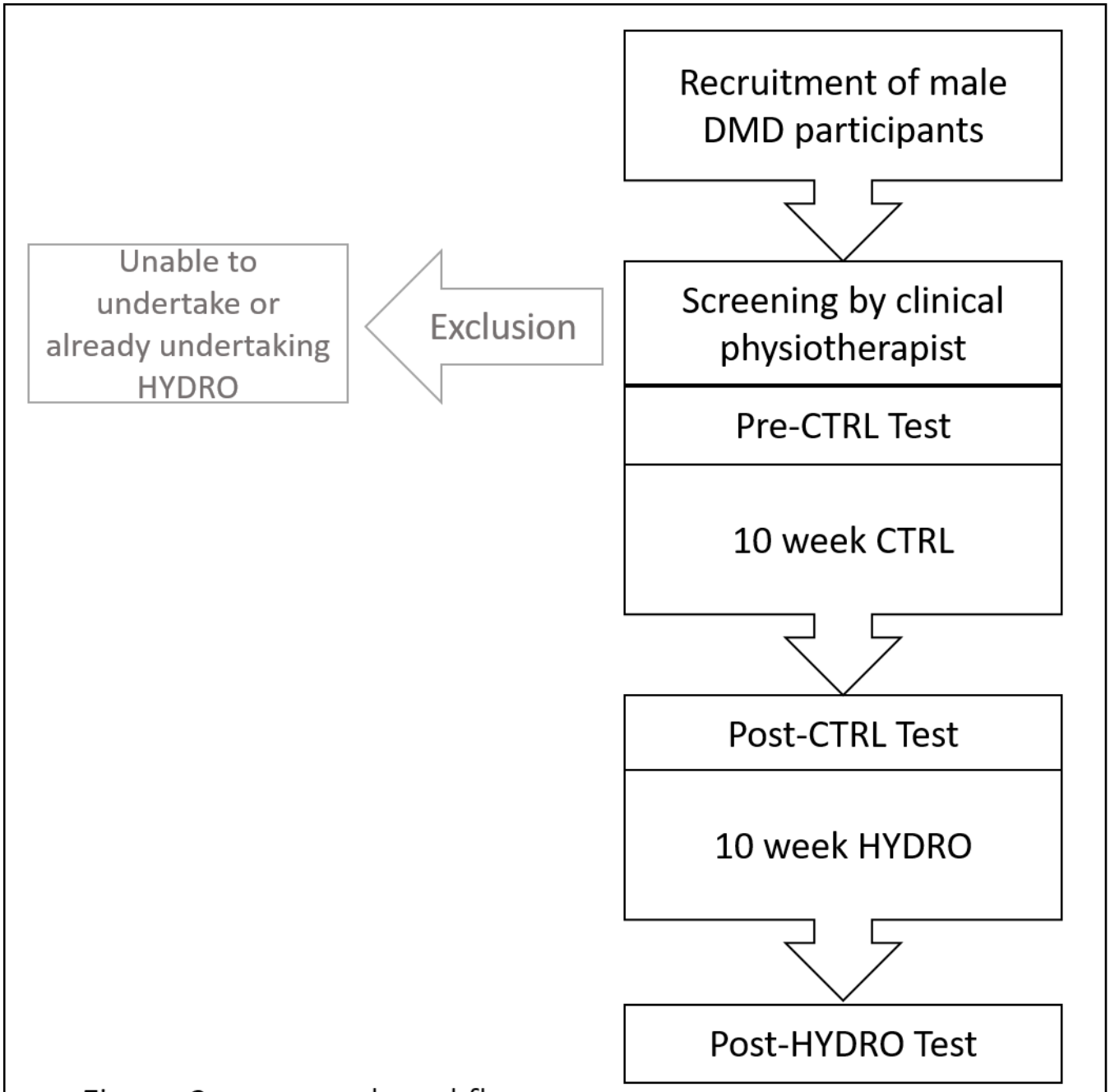

Figure 3: proposed workflow

Author	Age (years)	n	Condition	Training	Duration	Sessions	Outcome Measure
Vivas, 2011	Adults, 60 plus	11	PD	2/week, 45 mins	4 weeks	8	Berg balance (P<0.05) Functional reach test (P<0.05)
Dorval, 1996	10-17 yrs	10 & 10	CP	1/week, 55 mins	10 week	10	Self-esteem (P<0.05) Functional independence (P<0.05)
Salem, 2011	Adults,45-69 yrs	11	MS	2/ week, 60 mins	5 weeks	10	10m walk (P<0.05), Berg balance (P<0.05) Timed-up-and-go (P<0.05) Grip strength (P<0.05)
DeGoede/Morse	DMD 6+ yrs	32	DMD	1/week	12	12	QoL, Pain, Body composition
Gowans ,1999	Adults	39	FyM, OA, Back	2/week, 30 mins	7 weeks	14	6MW (P<0.05)
Ahern, 1995	Adult	72	OA/RA	4 day consecutive	(and 6 wk follow up)	16	QoL 4 day P<0.05 Pain 4 day P<0.05 Stiffness 6 week P<0.05
Fransen 2007	Adults	55	OA	2/week	12wk	24	QoL, Pain
Mannerkorpi, 2002	Adults, 45	28	FyM	1/week	6 mo	26	QoL SF36 (P<0.05, 5 of 8 scales, PF & BP)
Kesiktas, 2004		10 & 10	SCI-CP	3/week, 30min	10 weeks	30	Spasm severity P<0.05

Table 1: participant characteristics for neuromuscular conditions with hydrotherapy interventions. In grey our proposed study characteristics (Fym-Fibromyalgia, SCI-Spinal cord injury, OA-Osteoarthritis, MS-multiple sclerosis, CP-Cerebral Palsy, PD-Parkinson's disease, RA-rheumatoid arthritis).