# CLINICAL TRIAL PROTOCOL

This protocol has regard for the HRA guidance.

Full Title: **Clinical effectiveness of an adolescent-specific strengthening programme, compared to usual care, for ambulant adolescents with spastic cerebral palsy (ROBUST trial): a parallel group randomised controlled trial**

Short Title: Strengthening programme for ambulant adolescents with cerebral palsy (ROBUST)

Version 3.0_12Dec2024

Trial website:
https://www.ndorms.ox.ac.uk/research/clinical-trials/current-trials-and-studies/robust

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ROBUST_Protocol_
V3.0_12Dec2024
IRAS Project Number: 325313
REC Ref: 23/SC/0231

# Contents

## 1 RESEARCH REFERENCE NUMBERS

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|---|---|
| **Sponsor Protocol Number:** | PID16897 |
| **Clinical Trials Unit (CTU) Reference:** | OCTRU383 |
| **Funder Reference:** | NIHR135150 |
| **Ethics Reference Number:** | 23/SC/0231 |
| **IRAS Number:** | 325313 |
| **Registry:** | International Standard Randomised Controlled Trial Number (ISRCTN): 68282588 |
| **CPMS ID** | 57227 |

## 2 ORGANISATIONAL INFORMATION

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| **Chief Investigator (CI):** | Professor Sally Hopewell<br>University of Oxford<br><br>Refer to the KEY TRIAL CONTACTS section for contact details. |
| **Sponsor:** | University of Oxford<br><br>Refer to the KEY TRIAL CONTACTS section for contact details. |
| **Clinical Trials Unit:** | Oxford Clinical Trials Research Unit (OCTRU)<br>University of Oxford,<br>Botnar Research Centre,<br>Windmill Road,<br>Headington,<br>Oxford,<br>OX3 7LF.<br>E-mail: octrutrialshub@ndorms.ox.ac.uk<br><br>Clinical Trials Unit (CTU) Reference: 27<br><br>The trial is managed by the Surgical Intervention Trials Unit (SITU) group. |
| **Funder:** | The trial is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme. Refer to section 31.2 for full details of all funding sources. |
| **Co-applicants:** | The following are co-applicants on the trial grant and have contributed to the trial design and development of the protocol:<br><br>Prof Tim Theologis (University of Oxford)<br>Prof Jeremy Parr (Newcastle University)<br>Dr Morag Andrew (Newcastle upon Tyne NHS Foundation Trust)<br>Dr David Keene (University of Exeter)<br>Dr Jennifer Ryan (Royal College of Surgeons in Ireland)<br>Dr Lesley Katchburian (UCL Great Ormond Street Institute of Child Health)<br>Mrs Rachel Rapson (Torbay and South Devon NHS Foundation Trust)<br>Dr Ines Rombach (Sheffield University)<br>Dr Beth Fordham (University of Oxford)<br>Mr Gregory Firth (Maidstone and Tunbridge Wells NHS Trust)<br>Prof Daniel Perry (University of Liverpool)<br><br>**PATIENT AND PUBLIC CONTRIBUTORS**<br>Ms Vivi Gregory-Osborne<br>Mrs Helen Gregory-Osborne |
| **Additional protocol contributors:** | Dr Loretta Davies (University of Oxford) |

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| **Conflict of Interest statement:** | The following conflicts of interest have been declared by the protocol authors/contributors:<br>There are no potential conflicts of interest. |
| **Confidentiality Statement:** | In accordance with the NIHR Open Access policy, the protocol will be published and made freely and openly accessible to all. |

## 3 KEY TRIAL CONTACTS

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| **Trial Office/Coordinating centre for general queries** | ROBUST Trial Manager<br>Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences,<br>University of Oxford,<br>Botnar Research Centre<br>Windmill Road, Oxford<br>OX3 7LD<br><br>Tel: 01865 737643<br>E-mail: ROBUST@ndorms.ox.ac.uk |
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| **Trial Steering Committee (TSC) Chair:** | Mr Steve Cooke<br>University Hospitals Coventry & Warwickshire<br>Stephen.cooke@uhcw.nhs.uk<br><br>Other members of the TSC are detailed within a trial-specific TSC charter. |
| **Data and Safety Monitoring Committee (DSMC) Chair:** | Dr Jill Cadwgan<br>Evelina London Children's Hospital<br>Jill.Cadwgan@gstt.nhs.uk<br><br>Other members of the DSMC are detailed within a trial-specific DSMC charter. |

## 4 PROTOCOL APPROVAL/SIGNATORIES

This protocol has been approved by the Sponsor, Chief Investigator and Lead Statistician. Approval of the protocol is documented in accordance with OCTRU Standard Operating Procedures.

All parties confirm that findings of the trial will be made publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any important deviations and serious breaches of GCP from the trial as planned in this protocol will be explained.

## 5 LAY SUMMARY/PLAIN ENGLISH SUMMARY

Cerebral palsy (CP) is caused when babies around the time of their birth suffer brain injury from lack of oxygen in the brain. As they grow, children with CP develop stiff and weak muscles. They often have difficulty walking and moving and that makes it difficult for them to join in different activities. Exercises prescribed by Physiotherapists become a big part of their lives as it tries to train their muscles and help them participate in activities. When they reach their adolescent years and their body grows bigger the weakness of muscles in the legs becomes more of a problem. It is possible that a programme of exercises to strengthen their leg muscles could help them remain more active. We are not certain that young people with CP truly benefit from the time and effort they dedicate to doing these exercises. We are also not sure if this exercise might cause them too much discomfort and muscle soreness to be able to carry it out long-term.

The aim of this trial is to assess if an exercise programme to strengthen the muscles of young people with cerebral palsy is better than their usual physiotherapy treatment. We have developed an exercise programme, using resistance exercises, to strengthen the leg muscles in adolescents with CP. We paid particular attention in putting together a programme that could be accessible to adolescents from a wide range of backgrounds and be delivered through the NHS, if it proves to make a difference. We also want to make it interesting and fun so that young people will be happy to follow it for a long time. For instance, we will use interactive technology to engage and motivate the participants.

We will recruit adolescents with CP through the Cerebral Palsy Integrated Pathway (CPIP). This is the established NHS network of physiotherapists who monitor and treat young people with CP in the community. A computer will decide which half of the recruited adolescents will receive the new exercise programme. The other half will be offered advice and guidance from a physiotherapist to continue with their usual fitness or physical activity programme, not focusing on strengthening. The strength exercise programme will last about 4 months. At 6 and 12 months we will ask the participants with their parent/guardian to complete a standard scoring questionnaire that asks about their walking and ability to carry out their daily activities.

A young person with CP and their parent are part of the research team. They have advised on design of the exercise programme and research plan methods. We have also discussed our plans with a wider group of parents and adolescents to seek advice on specific areas. For example, how to motivate young people and monitor how they are getting on with the exercises. During the research, we will form a young people and parent advisory group to advise us throughout the trial and to help us make the results as widely known as possible at the end of the trial.

Results of this trial will be widely spread. We will present reports at conferences and publish in medical journals. We will also make the trial accessible to the general public by engaging with social media, producing explainer videos and using information graphics. We hope that the results we produce will be adopted widely by health professionals and help policy makers develop national guidelines for the physiotherapy treatment of adolescents with CP.

## 6 TRIAL SYNOPSIS

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| **Full Trial Title:** | Clinical effectiveness of an adolescent-specific strengthening programme, compared to usual care, for ambulant adolescents with spastic cerebral palsy (ROBUST trial): a parallel group randomised controlled trial |
| **Short Title:** | Strengthening programme for ambulant adolescents with cerebral palsy (ROBUST) |
| **Trial Acronym:** | ROBUST |
| **Trial Design:** | The ROBUST trial is a multi-centre, two arm, parallel design, superiority, randomised controlled trial. The participants will be individually randomised (1:1) to receive either a strengthening intervention programme or usual NHS care.<br><br>We will also embed a 'Study Within A Trial' (SWAT) to the ROBUST trial, to assess the effectiveness and cost-effectiveness of monetary incentives for increasing participant retention rates (see Section 11 and Appendix 3 for details). |
| **Trial Aim:** | To assess the clinical effectiveness of an adolescent-specific strengthening programme, compared to usual care, for ambulant adolescents with spastic cerebral palsy. |
| **Trial Participants/Target Population:** | The ROBUST trial will recruit adolescents from 12 to 18 years of age (i.e. from their 12$^{th}$ to their 18$^{th}$ birthday) with a diagnosis of spastic cerebral palsy (bilateral or unilateral) Gross Motor Function Classification System (GMFCS) levels I–III who are able to comply with assessment procedures and exercise programme with or without support from their carer.<br><br>There are defined guidelines for muscle strengthening through progressive resistance exercise in typically developing young people (15). A survey of current practice in the UK showed that strengthening exercises are one of the interventions frequently used by physiotherapists in adolescents with CP (8). However, there is wide variability in the strengthening exercises used and the regimens are primarily based on guidelines for people without CP (16). A Cochrane review of exercise interventions for CP found low-quality evidence that resistance training may improve muscle strength, but does not improve motor function, gait speed or participation in the short or intermediate term. However, all of the trials were small, resulting in considerable uncertainty; large, high quality randomised trials were recommended (17). A recent systematic review showed that resistance training improved motor function in children with CP. Trials included in this review were again small and heterogeneous in the exercise programme and choice of comparator (18). |

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| | The type of strengthening intervention used in the above trials ranged from weight training to multi-joint body weight or weight-loaded functional exercises (e.g. sit to stand, lunging, step-ups, side stepping, squatting) (17). Settings included the home, clinic or educational setting and duration varied between 4-20 weeks. Most published interventions were delivered with the frequency of 3 sessions per week. Programmes were individually tailored, based either on adjusting weight loading according to body weight or on the individual's ability to undertake a pre-defined number of repetitions. Most studies included gradual progression of the programme to increased weight loading and/or number of repetitions. The STAR trial, published most recently in 2020 (19), evaluated the effect of a 30 session (10 supervised and 20 unsupervised home based) resistance training programme compared to usual care in adolescents with CP and found no difference on gait efficiency, activity, and participation. However, again this trial was small (n=68) and the exercises included in this programme only targeted one specific muscle group, the ankle plantar flexors. We have learned from the STAR trial experience and the literature that a strengthening intervention focused on functional improvement should be targeting multiple muscle groups. The intervention should be deliverable within the NHS settings in a way that would motivate young people and would enhance long-term application.<br><br>None of the trials to date have included a behavioural change component. A strengthening intervention can only be effective if the target population perform and maintain the proposed exercise behaviours. There is evidence to suggest that the addition of behaviour change components to physical activity interventions increases the likelihood that the target population will perform the prescribed exercises (20). The capability-opportunity-motivation model of behaviour change (21) provides a theoretically based framework for designing complex interventions incorporating behaviour change in order to enhance behaviour change. Given the resources, time and effort (for young people, parents and professionals) required to deliver strengthening regimes, there is pressing need to evaluate clinical effectiveness (11, 13). The literature supports testing a clearly defined strengthening intervention that is acceptable to young people and families, widely supported by physiotherapists and deliverable in the NHS. As highlighted by NICE guidance CG145 on management of spasticity in young people (22), the intervention should be adolescent-centred and focused on activity and participation goals (13). The burden on the young person and family should be minimised and delivery of the intervention should be as unobtrusive as possible.<br>OBJECTIVES AND OUTCOME MEASURES of the main body of the protocol for full eligibility criteria. |
| **No. of trial arms:** | 2 |
| **Intervention:** | **Progressive resistance exercise programme**<br>Participants receive an individually tailored strengthening programme, including structured resistance exercises and advice, overseen by a physiotherapist with 6 one-to-one sessions over 16 weeks. |

<table>
<tr><td>Comparator:</td><td colspan="2">Usual NHS care<br>Participants receive an assessment with a physiotherapist and are provided with NHS advice on self-management, including access to supporting information and continuation of any usual exercise, fitness/physical activity programme (as applicable).</td></tr>
<tr><td>Planned Sample Size:</td><td colspan="2">334</td></tr>
<tr><td>Target no. of research sites:</td><td colspan="2">Approx. 12</td></tr>
<tr><td>Planned trial period:</td><td colspan="2">44 months</td></tr>
<tr><td>Planned recruitment duration:</td><td colspan="2">Recruitment is expected to last for 20 months.</td></tr>
<tr><td>Duration of intervention/treatment:</td><td colspan="2">Participants randomised to the intervention (strengthening programme) will have 6 sessions with a physiotherapist over 16 weeks. Participants randomised to usual NHS care will have a usual care advice session with a physiotherapist.</td></tr>
<tr><td>Follow-up duration:</td><td colspan="2">Each participant will be followed up for 12 months from randomisation.</td></tr>
<tr><td></td><td>Objective</td><td>Outcome Measure</td></tr>
<tr><td>Primary objective and outcome measure:</td><td>To assess whether an individually tailored strengthening programme overseen by a physiotherapist over 16 weeks, improves functional mobility in ambulant adolescents with spastic CP compared with usual care</td><td>Functional mobility at 6 months measured using the patient/parent reported GOAL (Gait Outcomes Assessment List) questionnaire</td></tr>
<tr><td>Secondary objectives and outcome measures:</td><td colspan="2">There are defined guidelines for muscle strengthening through progressive resistance exercise in typically developing young people (15). A survey of current practice in the UK showed that strengthening exercises are one of the interventions frequently used by physiotherapists in adolescents with CP (8). However, there is wide variability in the strengthening exercises used and the regimens are primarily based on guidelines for people without CP (16). A Cochrane review of exercise interventions for CP found low-quality evidence that resistance training may improve muscle strength, but does not improve motor function, gait speed or participation in the short or intermediate term. However, all of the trials were small, resulting in considerable uncertainty; large, high quality randomised trials were recommended (17). A recent systematic review showed that resistance training improved motor function in children with CP. Trials included in this review were again small and heterogeneous in the exercise programme and choice of comparator (18).<br><br>The type of strengthening intervention used in the above trials ranged from weight training to multi-joint body weight or weight-loaded</td></tr>
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| | functional exercises (e.g. sit to stand, lunging, step-ups, side stepping, squatting) (17). Settings included the home, clinic or educational setting and duration varied between 4-20 weeks. Most published interventions were delivered with the frequency of 3 sessions per week. Programmes were individually tailored, based either on adjusting weight loading according to body weight or on the individual's ability to undertake a pre-defined number of repetitions. Most studies included gradual progression of the programme to increased weight loading and/or number of repetitions. The STAR trial, published most recently in 2020 (19), evaluated the effect of a 30 session (10 supervised and 20 unsupervised home based) resistance training programme compared to usual care in adolescents with CP and found no difference on gait efficiency, activity, and participation. However, again this trial was small (n=68) and the exercises included in this programme only targeted one specific muscle group, the ankle plantar flexors. We have learned from the STAR trial experience and the literature that a strengthening intervention focused on functional improvement should be targeting multiple muscle groups. The intervention should be deliverable within the NHS settings in a way that would motivate young people and would enhance long-term application.<br><br>None of the trials to date have included a behavioural change component. A strengthening intervention can only be effective if the target population perform and maintain the proposed exercise behaviours. There is evidence to suggest that the addition of behaviour change components to physical activity interventions increases the likelihood that the target population will perform the prescribed exercises (20). The capability-opportunity-motivation model of behaviour change (21) provides a theoretically based framework for designing complex interventions incorporating behaviour change in order to enhance behaviour change. Given the resources, time and effort (for young people, parents and professionals) required to deliver strengthening regimes, there is pressing need to evaluate clinical effectiveness (11, 13). The literature supports testing a clearly defined strengthening intervention that is acceptable to young people and families, widely supported by physiotherapists and deliverable in the NHS. As highlighted by NICE guidance CG145 on management of spasticity in young people (22), the intervention should be adolescent-centred and focused on activity and participation goals (13). The burden on the young person and family should be minimised and delivery of the intervention should be as unobtrusive as possible.<br>OBJECTIVES AND OUTCOME MEASURES section of the main body of the protocol for full trial objectives and outcome measures. |

## 7 ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| APCP | Association of Paediatric Chartered Physiotherapists |
| AR | Adverse Reaction/Response |
| BACD | British Academy of Childhood Disability |
| BSCOS | British Society for Children's Orthopaedic Surgery |
| CI | Chief Investigator |
| COS | Core Outcome Sets |
| CPIP | Cerebral Palsy Integrated Pathway |
| CRF | Case Report Form |
| CTU | Clinical Trials Unit |
| DSMC | Data and Safety Monitoring Committee |
| GCP | Good Clinical Practice |
| GOAL | Gait Outcomes Assessment List |
| GMFCS | Gross Motor Function Classification System |
| GP | General Practitioner |
| HCRW | Health and Care Research Wales |
| HRA | Health Research Authority |
| HTA | Health Technology Assessment |
| ICF | Informed Consent Form |
| ISF | Investigator Site File |
| ISRCTN | International Standard Randomised Controlled Trials Number |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health and Care Research |
| OCTRU | Oxford Clinical Trials Research Unit |
| PI | Principal Investigator |
| PIC | Participant Identification Centre |
| PIS | Patient information sheet |
| PPI | Patient and Public Involvement |
| PROM | Patient Reported Outcome Measure |
| QA | Quality Assurance |
| REC | Research Ethics Committee |
| RGEA | Research Governance, Ethics & Assurance Team |
| REDCAP | Research Electronic Data Capture |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SITU | Surgical Intervention Trials Unit |
| SOP | Standard Operating Procedure |
| TIDieR | Template for Intervention Description and Replication |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| TUG | Timed Up and Go test |
| UKCRC | United Kingdom Clinical Research Collaboration |

## 8 BACKGROUND INFORMATION AND RATIONALE

### 8.1 Problem and diagnosis

Cerebral palsy (CP) encompasses a group of permanent developmental disorders affecting movement and posture and causing activity limitation. They are non-progressive disturbances occurring in developing fetal or infant brains (1). Whilst the primary lesion in the brain is static, the musculoskeletal consequences are progressive. CP affects approximately 1 in 400 children in the UK (2) and represents a lifetime disability with significant socio-economic consequences. Functional mobility is best classified by the Gross Motor Function Classification System (GMFCS), an international standard based on the severity of the motor disability (3). About 65% of children with CP are ambulant, either with walking aids (GMFCS level III) or without (GMFCS levels I and II). CP is also classified according to the affected body areas (one side of the body (hemiplegia), predominantly the lower limbs (diplegia) or all four limbs (quadriplegia)) and the neurological pattern (spastic, dyskinetic, ataxic, mixed) (1).

In 70% of cases, CP predominantly causes spasticity (increased muscle stretch reflex activity and passive stiffness). The increased muscle tone leads to progressive muscle stiffness and deficient longitudinal muscle growth (4). This, in turn, causes secondary joint contracture, bone deformity and pain (5). In addition to the stiffness caused by spasticity there is underlying muscle weakness, which contributes significantly to the motor function impairment (6). Motor development in spastic CP progresses until age 7 years and then levels off (7). In adolescence, the increase in body mass challenges lower limb function as problems with muscle weakness become more evident. This leads to decline in motor function, with impact on activity and participation (3). Improving or maintaining strength of lower limb muscles is therefore important in adolescence to minimise functional decline (8). Physiotherapy is introduced early in CP management to support motor development and prevent musculoskeletal problems (9). Physiotherapy provision throughout childhood represents significant time and cost for the child, family and NHS. Strengthening is more often used by the physiotherapists treating older children and adolescents with CP as it requires greater collaboration and compliance (10).

### 8.2 Justification for undertaking this research

Optimisation of therapy provision for children and young people with CP was a top priority in the British Academy of Childhood Disability (BACD) James Lind Alliance Childhood Disability Priorities Setting Partnership (JLA PSP) (11). This specific topic was identified as a top therapy research priority at a series of workshops led by the BACD Strategic Research Group, in partnership with NIHR HTA. Research on the effectiveness of physiotherapy in preventing deformity and the need for surgery was also prioritised by the British Society for Children's Orthopaedic Surgery -BSCOS in a JLA PSP on paediatric orthopaedic surgery (12). A recent scoping review funded by NIHR HTA highlighted the need for evidence-based physiotherapy interventions in young people with CP, which are deliverable through the NHS and focused on improving activity and participation in a child and family friendly manner (13).

The need to pursue research in this field is strongly supported by the CPIP (Cerebral Palsy Integrated Pathway) Physiotherapy Network, which monitors children with CP nationally (14). CPIP is funded by the NHS in England and supported by a national network consisting of members of the Association of Paediatric Chartered Physiotherapists (APCP), BACD and BSCOS. All children with CP are offered an annual CPIP musculoskeletal assessment by a community physiotherapist and standardised clinical examination data are collected. Not all people with CP attend hospital but they are almost invariably under the care of a community physiotherapist. Therefore, CPIP offers a unique opportunity to identify children with CP in the community, particularly in underserved areas where access to hospital-based services may be challenging.

This definitive randomised controlled trial, will use a parallel group design, to assess the effectiveness of an individually tailored strengthening programme overseen by a physiotherapist and compared to usual care in ambulant adolescents with spastic CP. Importantly, the intervention has been designed to ensure deliverability within the NHS setting.

**8.3 Choice of comparators**

There are defined guidelines for muscle strengthening through progressive resistance exercise in typically developing young people (15). A survey of current practice in the UK showed that strengthening exercises are one of the interventions frequently used by physiotherapists in adolescents with CP (8). However, there is wide variability in the strengthening exercises used and the regimens are primarily based on guidelines for people without CP (16). A Cochrane review of exercise interventions for CP found low-quality evidence that resistance training may improve muscle strength, but does not improve motor function, gait speed or participation in the short or intermediate term. However, all of the trials were small, resulting in considerable uncertainty; large, high quality randomised trials were recommended (17). A recent systematic review showed that resistance training improved motor function in children with CP. Trials included in this review were again small and heterogeneous in the exercise programme and choice of comparator (18).

The type of strengthening intervention used in the above trials ranged from weight training to multi-joint body weight or weight-loaded functional exercises (e.g. sit to stand, lunging, step-ups, side stepping, squatting) (17). Settings included the home, clinic or educational setting and duration varied between 4-20 weeks. Most published interventions were delivered with the frequency of 3 sessions per week. Programmes were individually tailored, based either on adjusting weight loading according to body weight or on the individual's ability to undertake a pre-defined number of repetitions. Most studies included gradual progression of the programme to increased weight loading and/or number of repetitions. The STAR trial, published most recently in 2020 (19), evaluated the effect of a 30 session (10 supervised and 20 unsupervised home based) resistance training programme compared to usual care in adolescents with CP and found no difference on gait efficiency, activity, and participation. However, again this trial was small (n=68) and the exercises included in this programme only targeted one specific muscle group, the ankle plantar flexors. We have learned from the STAR trial experience and the literature that a strengthening intervention focused on functional improvement should be targeting multiple muscle groups. The intervention should be deliverable within the NHS settings in a way that would motivate young people and would enhance long-term application.

None of the trials to date have included a behavioural change component. A strengthening intervention can only be effective if the target population perform and maintain the proposed exercise behaviours. There is evidence to suggest that the addition of behaviour change components to physical activity interventions increases the likelihood that the target population will perform the prescribed exercises (20). The capability-opportunity-motivation model of behaviour change (21) provides a theoretically based framework for designing complex interventions incorporating behaviour change in order to enhance behaviour change. Given the resources, time and effort (for young people, parents and professionals) required to deliver strengthening regimes, there is pressing need to evaluate clinical effectiveness (11, 13). The literature supports testing a clearly defined strengthening intervention that is acceptable to young people and families, widely supported by physiotherapists and deliverable in the NHS. As highlighted by NICE guidance CG145 on management of spasticity in young people (22), the intervention should be adolescent-centred and focused on activity and participation goals (13). The burden on the young person and family should be minimised and delivery of the intervention should be as unobtrusive as possible.

## 9 OBJECTIVES AND OUTCOME MEASURES

### 9.1 Aim

The aim of the ROBUST trial is to assess the clinical effectiveness of a strengthening programme, compared to usual care for ambulant adolescents with spastic cerebral palsy. Table 1 provides a summary of outcomes being assessed.

**Table 1: Summary of outcomes assessed**

| Outcome | Measurement | Time point(s) of evaluation of this outcome measure (post-randomisation*) |
|---|---|---|
| Functional mobility | Gait Outcomes Assessment List (GOAL) questionnaire (23). | 0, 6, 12 months |
| Muscle Strength (clinician assessed) | Five-time sit-to-stand test for adolescents with CP (24) | 0, 6 months |
| Motor Function (clinician assessed) | Timed up and Go test (25) TUG | 0, 6 months |
| Independence | GOAL subdomain A (23) | 0, 6, 12 months |
| Balance | GOAL subdomains A,B,D (23) | 0, 6, 12 months |
| Pain and discomfort | GOAL subdomain C (23) | 0, 6, 12 months |
| Health-related quality of life | EQ-5D-Y (26) | 0, 6, 12 months |
| Educational outcomes | Educational attendance record (days) | 0, 6, 12 months |
| Exercise adherence | Participant/Parent self-reported adherence | 6, 12 months |
| Additional physiotherapy treatment | Participant/Parent self-reported treatment | 6, 12 months |

*post-randomisation relates to 6 and 12 month time points

### 9.2 Primary objective and outcome measure

| Objective | Outcome measure | Time point(s) of evaluation of this outcome measure (if applicable) | Data required | Source data (including location) |
|---|---|---|---|---|
| To assess whether an individually tailored strengthening programme overseen by a physiotherapist over 16 weeks, improves functional mobility in ambulant adolescents with spastic CP | Functional mobility at 6 months measured using the patient/parent reported GOAL (Gait Outcomes Assessment List) | 6 months post-randomisation | Not applicable | Participant/parent-reported outcome (questionnaires administered and data collected centrally). |

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| compared with usual care | | | | |

**9.3 Secondary objectives and outcome measures**

| Objective | Outcome measure | Time point(s) of evaluation of this outcome measure (if applicable) | Data required | Source data (including location) |
|---|---|---|---|---|
| To investigate if there are any differences at 12 months in **functional mobility** with an individually tailored strengthening programme compared to usual NHS care. | Gait Outcomes Assessment List (GOAL) questionnaire. | 0, 12 months | Not applicable | Participant/parent-reported outcome (questionnaires administered and data collected centrally). |
| To investigate if there are any differences at 6 months in **muscle strength** (clinician/research staff assessed) with an individually tailored strengthening programme compared to usual NHS care. | Five-time sit-to-stand test for adolescents with CP. | 0, 6 months | eCRF | Clinician/research staff assessed |
| To investigate if there are any differences at 6 months in **motor function** (clinician/research staffassessed) with an individually tailored strengthening | Blinded, clinician/research staff-assessed Timed up and Go test TUG | 0, 6 months | eCRF | Clinician/research staff assessed |

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| programme compared to usual NHS care. | | | | |
| To investigate if there are any differences at 6 and 12 months in **independence** with an individually tailored strengthening programme compared to usual NHS care. | GOAL subdomain A | 0, 6, 12 months | Not applicable | Participant/parent-reported outcome (questionnaires administered and data collected centrally). |
| To investigate if there are any differences at 6 and 12 months in **balance** with an individually tailored strengthening programme compared to usual NHS care. | GOAL subdomains A,B,D | 0, 6, 12 months | Not applicable | Participant/parent-reported outcome (questionnaires administered and data collected centrally). |
| To investigate if there are any differences at 6 and 12 months in **pain and discomfort** with an individually tailored strengthening programme compared to usual NHS care. | GOAL subdomain C | 0, 6, 12 months | Not applicable | Participant/parent-reported outcome (questionnaires administered and data collected centrally). |
| To investigate if there are any differences at 6 and 12 months in **health-related quality of life** with an individually tailored strengthening programme | EQ-5D-Y | 0, 6, 12 months | Not applicable | Participant/parent-reported outcome (questionnaires administered and data collected centrally). |

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| compared to usual NHS care. | | | | |
| To investigate if there are any differences at 6 and 12 months in **educational attendance** with an individually tailored strengthening programme compared to usual NHS care. | Educational attendance record (days) | 0, 6, 12 months | Number of days absent from school. | Participant/parent-reported outcome (electronic or paper trial questionnaire) |
| To investigate if there are any differences at 6 and 12 months in **exercise adherence** with an individually tailored strengthening programme compared to usual NHS care. | Patient/Parent self-reported adherence | 6, 12 months | Frequency of completed exercises, duration of completed exercises | Participant/parent-reported outcome |
| To investigate if there are any differences at 6 and 12 months in **additional physiotherapy treatment** with an individually tailored strengthening programme compared to usual NHS care. | Patient/Parent self-reported adherence | 6, 12 months | Contact with physiotherapist, number of times participant has seen a physiotherapist (outside of the trial) | Participant/parent-reported outcome (electronic or paper trial questionnaire) |

**9.4 Choice of primary outcome/justification for the follow-up period**

The primary outcome is functional mobility at 6 months measured using the patient/parent reported GOAL (Gait Outcomes Assessment List) questionnaire (23). The GOAL is validated specifically for use in ambulant CP and is internationally accepted as the appropriate functional outcome measure for lower limb interventions in this population. It consists of 48 items grouped into 7 domains; A: activities of daily living and independence; B: gait function and mobility; C: pain, discomfort and fatigue; D: physical activities, sports and recreation; E: gait pattern and appearance; F: use of braces and mobility aids; G: body image and self-esteem. A total GOAL score will be calculated in line with the scoring manual, ranging from 0 to 100, with higher values indicating better outcomes.

We will use the child version of the GOAL whenever possible and the parent version one if not. The families will be asked to decide which version is most appropriate as part of the consent process and their decision will be recorded on the baseline clinical assessment form to enable consistent use of the same version throughout their trial participation. Our first choice will be to use the child version in order to allow adolescent's views to be heard. However, we will revert to the parent view when the adolescent is unable to complete the form. We believe that this is a reasonable compromise and any bias introduced by the use of the parent version in some participants will be eliminated through randomisation. We will be consistently using either the child or the parent version for each participant throughout the trial, i.e. at baseline, 6 and 12 months post-randomisation. For follow up the REDCap trial database will use this information to determine which questionnaire to email out, likewise, this data will be used to determine which version to send out in the post. If the participant and their parent/guardian completes the 6 month questionnaire in clinic, site staff will need to view the REDCap database which version is required.

### 9.5 Secondary outcomes

A clinician/research staff member blinded to treatment allocation will collect an objective measure of muscle strength measured using the Five-time sit-to-stand test for adolescents with CP and motor function using the Timed up and Go test (24, 25)(40). Patient/parent reported outcomes include: independence measured using the GOAL subdomain A, balance measured using the GOAL subdomains A,B,D, pain and discomfort measured using the GOAL subdomain C (23) health-quality of life measured using the EQ-5D-Y (26), educational attendance based on educational attendance record to ensure this is not reducing as a result of the intervention, and exercise adherence. We considered different ways to assess educational outcomes and have previously consulted with teachers on this subject. The challenge that we identified in measuring educational attainment is that children span educational levels (i.e. Key Stage 3/KS4/KS5) and not all children will follow the national curriculum level (i.e. those with special educational needs who are working below the standard of the national curriculum tests and assessments). "Participation in learning" was identified (COS in this population) as a key outcome that could readily be measured. We will therefore record educational attendance, measured by days of educational absence, believing that we cannot usefully measure other educational outcomes. We will also record any additional physiotherapy treatment received outside of the trial.

### 9.6 Use of core outcome sets (COS)

There are no Core Outcome Sets (COS) developed specifically for physiotherapy interventions in ambulant children and adolescents with CP. However, a COS has recently been developed for lower limb surgical interventions in this population where the GOAL has been recommended (27). One of the main aims of physiotherapy in this population is to reduce musculoskeletal impairment to improve activity and participation. Prevention of deformities reduces the risk of surgery, thus it is appropriate to consider this COS for this trial. Our choice of primary and other outcome measures has also been informed by qualitative interviews with young people and their parents (28) and our PPI group. Patient/parent-reported outcomes, including educational attendance (participation in learning), will be assessed at baseline, 6 and 12 months. Clinician/research staff member assessed outcomes of muscle strength and motor function will be assessed at baseline and 6 months.

## 10 TRIAL DESIGN AND SETTING

The ROBUST trial is a multi-centre, two arm, parallel design, superiority, randomised controlled trial with an embedded internal pilot (first 6 months of recruitment). The participants will be individually randomised (1:1) to receive either the ROBUST strengthening programme or usual NHS physiotherapy care.

The trial (including the internal pilot) aims to recruit and randomise 334 adolescents (167 in each arm) with a diagnosis of spastic cerebral palsy (bilateral or unilateral) from approximately 12 sites in the UK providing NHS CP care. Participants will be randomised to receive a strengthening programme consisting of an individually tailored strengthening programme overseen by a physiotherapist via 6 one-to-one sessions over 16 weeks, or to usual NHS physiotherapy care. Usual NHS care involves an assessment with a physiotherapist with NHS advice on self-management, including access to supporting information and continuation of any usual exercise, fitness/physical activity programme (as applicable).

Participants will be identified through the Cerebral Palsy Integrated Pathway (CPIP) Network (14) and recruited from NHS Trusts / NHS Health Boards, providing care for children and young people with CP, where they will be assessed for eligibility by the clinical team, both supported by the local PI and research team in case of uncertainty. All children with CP are offered an annual CPIP musculoskeletal assessment by a community physiotherapist. Not all people with CP attend hospital, therefore CPIP offers a unique opportunity to identify children with CP in the community, particularly in underserved areas where access to hospital-based services may be challenging. This method will support recruitment of as representative sample of young people with CP as is possible.

Participants randomised to the strengthening programme will receive an individually tailored, strengthening programme overseen by a physiotherapist over 6 one-to-one sessions across a 16 week period. The first physiotherapy session will be up to 90 minutes followed by 5 additional sessions of up to 60 minutes. Sessions will be in an outpatient setting according to clinical need and local service provision.

Participants randomised to the strengthening programme will also be given access to a trial website where they can access ROBUST specifically developed advice materials. The young person and their parent/guardian will be given access to the appropriate set of exercises (pre-selected by their physiotherapist from a library of exercises). If the participant would prefer paper copies instead, the exercises can be inserted by the physiotherapist into their participant pack.

Participants randomised to usual NHS care will attend for a single session with a physiotherapist for an assessment, lasting up to 90 minutes. Participants and their parent/guardian will be provided with current NHS advice on self-management, including access to supporting information and continuation of any usual fitness/physical activity programme (as applicable).

Physiotherapists delivering usual care will be different to those delivering the ROBUST strengthening programme, where possible.

A trial flow chart is provided in APPENDIX 1 –TRIAL FLOW CHART.

We are embedding a SWAT (Study Within A Trial) to potentially assist with follow up questionnaire completion rates. The SWAT will assess the effectiveness and cost-effectiveness of monetary incentives for increasing participant retention rates (see Section 11 for more information and Appendix 3 for further details of the SWAT protocol).

### 10.1 Recruiting sites/site types

Participants will be recruited from at least 12 UK organisations (NHS Hospital Trusts/NHS Health Boards) providing NHS CP care.

### 10.1.1 Participant Identification Centres (PICs)

Paediatric community physiotherapy services (through the CPIP Network) may act as PICs (Participant Identification Centres) sites in identifying potentially eligible participants, depending on set up of local services.

## 10.2 Collection of outcome data and follow-up assessments

All participants, with the support of their parent/guardian will be asked to complete a baseline questionnaire (electronically or on paper) prior to randomisation. Clinical outcomes (i.e. muscle strength and motor function) will be assessed at the initial visit.

Patient-reported outcomes will be assessed using an electronic questionnaire (or paper, if requested) at 6 and 12 months post-randomisation.

Clinician/research staff member assessed outcomes will be assessed at a face to face clinic appointment at 6 months by a physiotherapist/assistant practitioner/research staff member who is blind to the treatment allocation and has not been involved in delivery of the intervention or usual care. Participants who do not attend this face to face clinic appointment will be contacted by phone by the local site team and a reminder appointment sent.

Refer to section 17 for full details of outcome data collection and follow-up assessments.

## 10.3 Countries of recruitment

UK

## 10.4 Duration of participant involvement

Participants will be in the trial for approximately 12 months from randomisation to last protocol visit.

## 10.5 Post-trial treatment/care and follow-up

Following a participant's final protocol visit, they will receive standard NHS care.

## 10.6 Use of Registry/NHS Digital data

Permission will be sought from trial participants or their parent/guardian/consultee/legal representative (for those 16+ years in Scotland who are unable to consent for themselves), as appropriate for collection of long-term follow-up (up to five years), using routinely collected NHS data (NHS England / Digital Health and Care Scotland), from baseline (i.e. from the time of consent/randomisation), to measure avoidance of surgery as a marker of treatment success. This is subject to the receipt of additional funding.

## 10.7 Health Economics

There are no health economic analyses to be undertaken as part of the trial.

## 10.8 Expected recruitment rate

The anticipated monthly recruitment rate is 2-3 participants per month per site. Six sites reviewed their physiotherapy clinic records (Oxford University Hospitals, Alder Hey Children's Hospital, Royal London Hospital, Sheffield Children's Hospital, Coventry and Warwick Hospital, Robert Jones and Agnes Hunt Orthopaedic Hospital) and identified a minimum of 10 to 12children with spastic cerebral palsy GMFCS levels I-III are reviewed through their site and their Community Physiotherapy Services per month. Based on our experiences of conducting other research studies in this population (CPinBOSS; IRAS ref: 259767, Standing up for CP; IRAS ref: 240760, STAR; IRAS ref: 172294) we believe it is realistic to anticipate recruitment of 2-3 participants per month from each site. Recruitment will be closely monitored against this target during the 6 month pilot phase and over the remaining 14

months of the recruitment period. Data from the internal pilot trial will inform any revisions about the number of sites and the timeline for the main trial.

### 10.9 Equality, diversity and inclusion for trial participants

We have considered the INCLUDE framework guidance (29) in designing the ROBUST trial protocol. Racial/ethnic and social diversity is important to ensure that the trial is based on a sample representative of the population served by the NHS. We will ensure that site recruitment includes socially deprived areas which are likely to have been underserved in the past. We will actively support sites who have not been involved in trials before. In discussion with our PPI partners, we will target recruitment at sites covering underserved and ethnically/racially diverse areas to ensure our sample is inclusive of those. As the recruitment basis for the ROBUST trial is with the community physiotherapy, rather than the hospital settings, this will ensure a broader reach and will help include populations that are not regularly represented in research studies. ınclusivity of participants is captured via demographic data options on the screening log and Baseline questionnaire.

The inclusion criteria are broad to ensure children with varied levels of impairment can participate. The trial processes include sharing trial information, obtaining consent and delivering the intervention in a way inclusive of children, regardless of impairment. Using animated video explainers (which include subtitles) provides a simple way to introduce the trial to a wide range of children and their parents. The introduction to the trial will also be supported by site staff who may not only be familiar with the young person and their parent/guardian but are experienced in conveying complex information to children with varied levels of impairment. Educational disruption will be minimised by offering physiotherapy sessions after school/educational attendance. As parent/guardian support and assistance is permitted in the delivery of the intervention, we will be able to include young people who may have a learning disability and/or behaviours that challenge. Where required, we will provide tablets to allow electronic media access to families that may not have such facilities at home or through their educational setting. The family's ability to access the internet will form part of the participant's baseline assessment. If required, a tablet computer enabled to access the internet will be loaned to participants and sent directly to the family from the Trial Office as part of the ROBUST strengthening programme to enable them to access the trial website during the supervised exercise period. In addition, we will be exploring translation requirements with sites, going forward. Families will also be reimbursed for reasonable travel expenses in line with the University of Oxford travel policy of reimbursement. This will cover travel to and from your trial appointments, if requested.

### 10.10 End of trial

The end of is the point at which all the data have been entered/received and all queries resolved. The trial will stop randomising participants when the stated number of patients to be recruited is reached.

The sponsor, funder and the Chief Investigator reserve the right to terminate the trial earlier at any time. In terminating the trial, they must ensure that adequate consideration is given to the protection of the participants' best interests.

## 11 SUB-STUDIES/TRANSLATIONAL STUDIES/MECHANISTIC STUDIES

We will embed a 'Study Within A Trial' (SWAT) to the ROBUST trial, to assess the effectiveness and cost-effectiveness of monetary incentives for increasing participant retention rates (as described in Appendix 3).

Participants will be randomised (1:1 ratio) to receive a £10 shopping voucher unconditionally prior to the 6- and 12-month follow-up time-points (intervention group); or a £10 shopping voucher

unconditionally prior to the 12-month follow-up time-point only (control arm). As part of the development of the SWAT, young people and their families, as part of our ROBUST Young Person / Parent Advisory Groups, have informed the decision to undertake this sub-study, as well as the type and value of the incentive.

## 12 PARTICIPANT ELIGIBILITY CRITERIA

Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the Principal Investigator.

### 12.1 Timing of eligibility assessment

Eligibility will be assessed upon initial entry into the trial and checked at the point of randomisation.

**Overall description of trial participants**

The ROBUST trial will recruit adolescents aged 12-18 years (i.e. from their 12$^{th}$ to their 18$^{th}$ birthday) with a diagnosis of spastic CP (bilateral or unilateral) GMFCS levels I–III who are able to comply with assessment procedures and exercise programme with or without support by their carer, and who are not regularly performing a structured exercise programme focused on resistance training as part of their usual NHS physiotherapy routine

Written informed consent must be obtained before any trial specific procedures are performed. Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the Principal Investigator (PI) based on the below criteria.

### 12.2 Inclusion Criteria

A patient will be eligible for inclusion in this trial if **ALL** of the following criteria apply:

- adolescent aged 12-18 years (i.e. from their 12th to their 18th birthday)
- diagnosis of spastic CP (bilateral or unilateral) GMFCS levels I–III
- willing for their community physiotherapy service and GP to be informed of their participation in the trial
- under 16: participant is willing to take part in the study and has a parent/guardian who is willing and able to give informed consent for the child's participation in the study.
- over 16: participant is willing and able to give informed consent or a Consultee (England and Wales) / Legal Representative (Scotland) can advise on behalf of the participant (see section 15.1)

### 12.3 Exclusion Criteria

A patient will not be eligible for the trial if **ANY** of the following apply:

- patient has had orthopaedic surgery of the lower limbs or selective dorsal rhizotomy in the past 12 months or planned (i.e. date confirmed) in the next 6 months
- patient has had lower limb botulinum toxin injections or serial casting in the past 4 months or planned (i.e. date confirmed) in the next 6 months
- patient is regularly performing a structured resistance exercise programme focused on resistance training as part of their usual physiotherapy routine
- patient is unable to comply with the assessment procedures and exercise programme with or without support by their parent/guardian

### 12.4 Rationale for inclusion and exclusion criteria

Inclusion and exclusion criteria are in line with the NIHR HTA programme commissioning brief (see Appendix 2). In addition, patients who have had orthopaedic surgery of the lower limbs or selective

dorsal rhizotomy in the past 12 months or planned in the next 6 month will be excluded as the results of the surgery could have a confounding effect on the effectiveness of the trial intervention. l. Similarly, patients who have had lower limb botulinum toxin injections or serial casting in the past 4 months or planned in the next 6 months will also be excluded.

### 12.5 Pre-trial screening tests or investigations

There are no pre-trial screening tests for inclusion in the trial.

### 12.6 Protocol waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of randomised trial. There will be no waivers regarding eligibility i.e. each participant must satisfy all the eligibility criteria. Changes to the approved inclusion and exclusion may only be made by a substantial amendment to the protocol.

Before entering a patient into the trial, the principal investigator or designee will confirm eligibility. If unsure whether the potential patient satisfies all the entry criteria and to clarify matters of clinical discretion research team members should contact the ROBUST Trial office, who will contact the Chief Investigator or designated clinicians as necessary. If in any doubt the Chief Investigator must be consulted before recruiting the patient. Details of the query and outcome of the decision must be documented in the Investigator Site File (ISF) /Trial Master File (TMF).

### 12.7 Clinical queries and protocol clarifications

Every care has been taken in drafting this protocol. Contact the ROBUST Trial Office for clarification if any instructions seem ambiguous, contradictory or impractical. Clinical queries must also be directed to the Trial Office. All clinical queries and clarification requests will be logged, assessed and a written response provided. Minor administrative corrections or clarifications will be communicated to all trial investigators for information as necessary. For urgent safety measures or changes that require protocol amendment see section 27.7.

## 13 SCREENING AND RECRUITMENT

### 13.1 Participant Identification

Potential participants could be identified and recruited during their routine paediatric, orthopaedic and physiotherapy clinic visits. The Cerebral Palsy Integrated Pathway (CPIP) Network (14) will also be used to identify potential participants. CPIP is a network covering the UK and ROI, all children with CP are offered an annual CPIP musculoskeletal assessment by a community physiotherapist. Not all people with CP attend hospital but they are almost invariably under the care of a community physiotherapist. Therefore, CPIP offers a unique opportunity to identify children with CP in the community, particularly in underserved areas where access to hospital-based services may be challenging.

To reflect the variation in regional NHS care provider set up there is a need for flexibility in how potential participants are identified and recruited. The regional set up will be explored on a site-by-site basis through the site feasibility process. One model, consistent with many established integrated care pathways is for the community paediatric physiotherapy NHS services to act as a PIC (via the CPIP assessment process) and referring to the nearest participating NHS site. In this instance, paediatric community physiotherapy services within the local area surrounding each trial site will be informed about the trial and encouraged to identify potentially eligible participants and provide information about the trial. Clinical teams will have the option of sending out information to potential participants ahead of or following their clinic visit. Standard text will be provided to the clinical team to include in a letter to the potential participant and their parent/guardian. If potential participants are interested, they would be referred to their nearest participating NHS site. Another potential model is for

secondary and community NHS services to be under one Trust/Board, in which they would represent together a single participating site for recruitment.

Participants will be fully assessed for eligibility and recruited through participating NHS sites. Posters advertising the ROBUST trial will also be displayed in the paediatric, orthopaedic and physiotherapy clinics to raise awareness of the trial with adolescents, their parents and clinicians. Participant Identification Centres (PICs) may be used to identify potential participants depending on the set up of local services. Clinical teams will have the option of sending out information/a letter to potential participants with details of who to contact if interested in participating.

Adolescents with a diagnosis of ambulant spastic CP (GMFCS levels I-III) (3) and who meet current indications for NHS physiotherapy as per NICE guidelines (22) will be screened for eligibility and given information about the ROBUST trial. There are several ways in which adolescents and their parent(s) will be approached depending on local service provision. These would include as part of their annual community physiotherapy CPIP review, any other CP clinical care attendance or contacted over the phone. If interested to know more, they may be:

1) Contacted by the recruiting site team to discuss further and arrange a full baseline visit at the recruiting NHS site where consent, questionnaire completion, baseline clinical assessment and randomisation can take place.

Or

2) Contacted by the recruiting site team using the appropriate study invite letter (Parent, 16-18 years or Consultee versions available) and appropriate PIL(s) and consent/assent/consultee declaration form (for more details on this remote consent option see Section 15: Informed Consent). This would be followed by a clinical baseline assessment and randomisation visit at the recruiting NHS site.

Since these children are already under the care of their nearest NHS Trust/Board, this would not constitute a new referral by NHS standards. Instead, identification of a new candidate would trigger the next hospital appointment.

If eligible (as described in Section 12) and in accordance with whichever approach was chosen from above,adolescents and their parents will be provided with developmental age-appropriate information about the trial, including an 'explainer video', 12-15 year olds PIL/16-18 year olds PIL/Parent/Guardian PIL (on behalf of 12-15 year olds) or Consultee PIL /Legal Representative PIL (Scotland)(on behalf of 16-18 year olds unable to consent for themselves) and a verbal explanation of the trial and trial procedures. The family will be given the opportunity to discuss issues related to the trial initially with their physiotherapist and/or a research team member supported by the local site principal investigator in case of uncertainty, as well as family and friends. The parent(s)/guardian or consultee/legal representative (Scotland) will then be asked to sign either a Parent/Guardian Consent Form or Consultee Declaration Form (whichever is applicable) and where appropriate, the adolescent will be asked for their assent or consent as appropriate for their age and developmental ability (as described in Section 15.1). This will then be countersigned by the relevant member of the site team. For the trial Consent Flowchart see section 15.1 below.

Patients who do not meet the inclusion criteria or who do not wish to participate will continue to receive their standard NHS physiotherapy treatment.

### 13.2 Re-screening if patient does not meet inclusion/exclusion criteria first time round

Not applicable for this trial

### 13.3 Use of screening logs

Screening logs will be used to record information about the number of patients considered and/or approached for the trial. Screening will be completed electronically using the Research Electronic Data Capture (REDCap) trial database. Personal identifiable data will not be recorded on the screening log; a screening log will be assigned to each patient screened. Anonymous information will be recorded on the age, ethnicity, deprivation index and sex of those who decline to participate so that we can assess the generalisability of those recruited. The reasons for declining will be asked and any answers offered will be recorded.

## 14 TRIAL INTERVENTION AND COMPARATOR

Eligible participants will be randomised to receive either the strengthening programme or usual NHS care. All of the physiotherapists delivering trial interventions, strengthening programme exercise sessions and usual care will have access to a comprehensive intervention manual and will be required to have undertaken trial-specific training, either face-to-face delivered at recruiting sites by a ROBUST trial research physiotherapist and/or via a training video (DVD or online using a personalised login). The trial research physiotherapists will be experienced practitioners, under the supervision of one of the physiotherapists on the central trial team. The training will include comprehensive guidance on the theory and practical delivery of the trial interventions.

### 14.1 Progressive resistance exercise programme (intervention)

The participants randomised to the progressive resistance exercise programme will receive an individually tailored, structured exercise and advice programme overseen by a physiotherapist over 6 one-to-one sessions over a 16 week period. This period of training allows time for the neurophysiological response to resistance training and for regular performance of exercises to become part of daily routine (30). An initial supervised period with the young person and providing parent/guardian training aims to initiate engagement in longer-term independent exercise. The first physiotherapy session will be up to 90 minutes followed by 5 additional sessions of up to 60 minutes and offered at times that minimise disruption to education, consistent with NHS care for this patient group. Appointments will be coordinated so that participants typically start their first exercise session within 2-4 weeks of randomisation, as per local appointment availability. Sessions will be in an outpatient setting or in the participants' home or educational setting according to clinical need and local service provision.

The strengthening intervention programme has been developed following a review of high quality evidence (31, 32), our previous work (19, 33) and consultation with an expert reference group and young people and parents. Resistance exercises targeting lower-limb muscle groups will be performed at home/educational setting with the assistance (as appropriate) of others involved in their care. As per evidence-based guidelines for resistance exercise and previous trial experience with this patient group (STAR trial), training volumes will be set to optimise the neuromuscular adaptation to overload and performed three times a week (15, 19, 34) on non-consecutive days. Setting exercise intensity and load will be facilitated by use of the modified Borg scale of perceived exertion, an 11-point version of the Rating of Perceived Exertion (RPE) scale (35) validated for quantifying the intensity of resistance exercise (36) this will include child friendly scale descriptors. Weighted vests and resistance exercise bands will be used to enable adequate loading without relying on expensive gym-based equipment.

The programme will follow the principles of progression for resistance exercises. Consistent with feedback from our clinical expert and PPI groups and previous qualitative work on exercise

prescription for people with cerebral palsy (37), the participant and physiotherapist will jointly choose up to five exercises options based on the specific needs identified during the assessment and based on the participants functional mobility level (GMFCS I-II and III), while ensuring the exercise progression principles are consistent and monitored carefully. Our PPI and expert reference group identified that providing the participants with a range of exercises they can choose from is important to ensure adherence to the intervention. The number and type of exercises will be recorded using treatment logs maintained on the trial website by the trial physiotherapists.

To support adherence to the exercise intervention and following the advice of our PPI partners all participants will have access to written instructions on the progressive resistance exercises chosen, including photos of each exercise and video instructions of the progressive resistance exercises chosen hosted on a web-based adolescent friendly platform.

To ensure accessibility, tablet computers will be loaned to participants to enable them to use the trial intervention website during the supervised exercise period, if families do not have access to such facilities at home. The family's ability to access the internet will form part of the participant's first physiotherapy session. If they need a tablet computer then one will be sent to them directly from the Trial Office and assigned to them for the 4 months of the intervention. Participants will be able to contact their physiotherapist over the phone/videoconference for support with their exercise programme or accessing online materials outside of scheduled sessions if needed, this extra contact will be monitored as part of intervention fidelity.

#### 14.1.1 Behavioural change strategies to encourage adherence

The intervention design and long-term behaviour change implementation will be underpinned by the capability-opportunity-motivation model of behaviour (COM-B) change for intervention development (21). Modifiable behavioural targets were identified from a systematic review of barriers to physiotherapy adherence, including in-treatment exercise adherence, low self-efficacy, greater perceived barriers to exercise, and pain levels during exercise (38). Resistance exercises can be uncomfortable. Previous qualitative work involving people with cerebral palsy highlighted the value of ensuring quality feedback and facilitated self-monitoring on progress to support exercise adherence (19).

The programme will include goal-setting and exercise diaries via the trial website, with joint problem-solving, monitoring and motivation from the physiotherapist. Of the behaviour change techniques, several components are core parts of usual physiotherapy practice and others included aim to encourage standardisation of relatively simple techniques, such as encouraging joint problem-solving and formally planning where and when to do prescribed exercises. The goal setting and exercise diaries are for use between the participant and their physiotherapist and will be reviewed at each physiotherapy session.

Refinements of the final intervention materials have also been informed by a workshop with PPI and clinical collaborators. The techniques we have included either have a supporting evidence base (39), have been implemented successfully in other trials (40), or align with recommendations in the NHS Health Trainer Handbook (41). Based on our experience of delivering previous physiotherapy trials of exercise interventions, which also included these behaviour change techniques, we are confident that 1 day training is sufficient. The volume of physiotherapy supervision is consistent with current practice in CP and existing NHS commissioning paradigms (22). Importantly, the intervention has been designed to ensure deliverability within the NHS setting.

### 14.2 Usual NHS care (usual care/comparator)

Adolescents allocated to usual care will attend for a single session with a physiotherapist for an assessment, lasting up to 90 minutes. Appointments will be coordinated so that participants typically receive their assessment session within 2-4 weeks of randomisation, as per local appointment availability. To avoid contamination physiotherapists delivering usual care will be different to those delivering the progressive resistance exercise intervention programme, where possible. Participants and their parent/guardian will be provided with NHS advice on self-management, including a participant information booklet on exercise and activity for young people with CP and continuation of any usual fitness/physical activity programme (as applicable) (22).

Participants allocated to the usual care group will not have access to the specific strengthening programme of the intervention group. Usual care will be recorded using a treatment log maintained on the trial website by the trial physiotherapists. A guideline on what is considered usual NHS care will be provided to the Physiotherapists delivering it and they will be trained to understand the components of this, to ensure they know the boundary of provision. The advice of the physiotherapists on delivery of usual care will be based on a recent mixed-methods consensus trial on usual physiotherapy in the UK for ambulant children and adolescents with CP (42). This highlighted that participation in sport and activity should form an important part of usual care. There was moderate agreement that task specific training and functional activity (e.g. gait training, practicing balance) should also be included in usual care. There was low level agreement on whether prolonged passive stretching, flexibility exercises, strength training or postural stability and balance exercises should be included in usual care.

### 14.3 Concomitant care

All participants will be advised they should maintain their usual physiotherapy care, which may include use of orthotics, and may seek other forms of treatment during the trial (as long as this does not include a progressive resistance exercise programme) but will be informed they should use usual routes (predominantly NHS referral) to do so. We will record and monitor any additional physiotherapy received outside of the trial intervention and prescribed during the trial follow up period.

### 14.4 Adherence to treatment

We will monitor adherence to treatment (participants undertaking the prescribed number of sessions and exercises), by logging aspects of the intervention. This will include the name of the exercises prescribed, the duration of physiotherapy appointments attended (and any additional contact), the number of sessions per week undertaken at home without physiotherapy supervision and whether the session was completed, partially completed or not completed. Treatment logs will be maintained on the trial website by both the trial physiotherapists, the participant and their parent/guardian. At 6 and 12 months of follow-up we will also record longer term self-reported adherence.

### 14.5 Intervention Fidelity

A rigorous quality control programme will be conducted to ensure protocol and intervention fidelity (i.e. the exercises being undertaken according to the protocol). Quality assurance checks will be made by the trial team, who will observe treatment sessions for physiotherapists. Site visits will be conducted periodically (minimum one visit per site per year) to observe the recruitment, consent and randomisation procedures, data collection, follow-up assessments, intervention and usual care session(s). The central trial team physiotherapists will gain permission for site visits with the use of research passports. Data will be collected on intervention delivery and exercise prescription to facilitate monitoring and reporting. Site staff will be requested to seek consent from an individual participant and their parent/guardian/consultee prior to a monitored session. CRF monitoring of intervention fidelity and discussions with site physiotherapists to gain feedback on their experiences

of the intervention protocols will also be undertaken. The responsibility for intervention quality control will be shared with the local site coordinating physiotherapist. The sites will regularly receive feedback from quality control visits as part of the strategy to maintain and improve fidelity. Any issues identified will be addressed by engaging the site staff in additional training and by increasing the intensity of monitoring by the central trial team. If issues persist, they will be escalated to the trial oversight committees.

The strengthening intervention programme will be manualised and staff will be trained to enhance standardisation of trial procedures. To avoid contamination we will ensure physiotherapists trained to deliver the progressive resistance exercise intervention will only deliver this treatment protocol, where possible. Physiotherapists delivering usual NHS care will be trained to understand the components of this, to ensure they know the boundary of provision. All participants and parents/guardian/consultee (intervention and control) will be educated on the importance of treatment fidelity and adherence to the intervention. Participants and their parents/guardian/consultee will be advised on the importance of adhering to the intervention to which they have been randomised.

## 15 INFORMED CONSENT

### 15.1 Consent Procedure

After the participants have initially been assessed for eligibility, informed consent will be sought and if a person (and/or their parent/guardian) approached is willing to give consent it will be collected by a member of the site trial team listed on the delegation log from each participant before they undergo any trial-related procedures or interventions related to the trial. Potential participants will be given the option of consenting remotely, if unable to attend in person. A member of the site research team will explain the details of the trial in addition to the already presented Participant Information Leaflet, ensuring that the potential participant and their parent/guardian has sufficient time to consider participating or not. A member of the site research team (authorised to do so on the delegation log) will answer any questions that the potential participant and their parent/guardian has concerning trial participation.

Informed consent will be obtained in line with NHS Health Research Authority guidance (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/research-involving-children/) for research involving children.

For adolescents aged under 16 years, their parent/guardian will be provided with the Parent/Guardian PIL and asked to sign the Parent/Guardian Consent Form (on behalf of adolescents aged 12-15 years), and the adolescent will be invited to sign an assent form. Assent will be taken where appropriate, however the absence of assent does not exclude the patient from the trial if consent has been obtained from the parent/guardian, and the child is not developmentally able to provide assent. If any adolescent indicates dissent or indicates they do not want to take part, they will not be included in the trial.

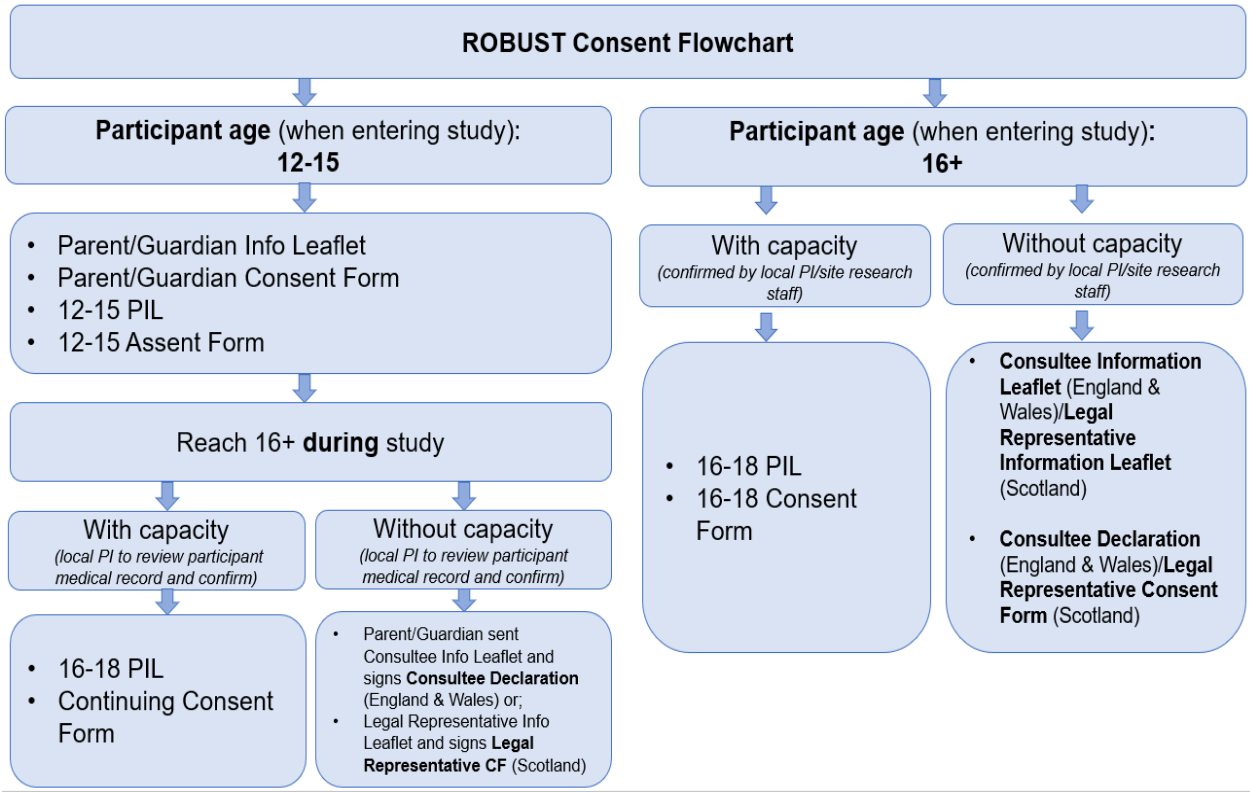
For adolescents aged 16 years and over and deemed to be competent to give consent to participate (based upon their capacity to understand the specific circumstances and details of the research being proposed), they will be provided with the 16-18 year olds PIL and asked to sign the 16-18 Year Olds Consent Form and give their own consent to participate.

For adolescents in England or Wales aged 16 years and over and deemed not to be competent to give consent to participate (by a healthcare professional in accordance with the Mental Capacity Act 2005), agreement will still be sought from the adolescent, with additional advice from their personal

consultee (which may still be the parent/guardian or another close relative or friend) on whether the adolescent should take part and what their wishes and feelings would be about taking part. The parent/guardian (or other relative/friend, if applicable) will be asked to sign a Consultee Declaration form. With agreement from the consultee, assent from the participant will also be obtained where appropriate.

For adolescents in Scotland aged 16 years and over and deemed not to be competent to give consent to participate (by a healthcare professional in accordance with the research provisions of the 2000, Adults with Incapacity Act), agreement will still be sought from the adolescent, with additional advice from their legal representative. The young person's legal representative may be one of the following: 1) a court appointed guardian or if they do not have one, then 2) someone with welfare power of attorney or if they do not have one, then 3) their nearest relative. Advice will be sought from the young person's legal representative on whether they should take part and what their wishes and feelings would be about taking part. They will then be asked to sign a Legal Representative Consent Form. With agreement from the legal representative, assent from the participant will also be obtained where appropriate.

See below for the trial Consent Flowchart.




### 15.2 Completion of the Informed Consent Form

The parent/guardian and the Investigator (or authorised designee) must personally sign and date the current approved version of the informed consent form.

The Informed Consent Form will usually be offered in clinic as an electronic form on a tablet device (with the consent/assent form being filled in directly on the trial database, REDCap), however paper consent/assent forms will also be made available for use in situations where electronic consent is not possible or suitable. The paper consent/assent form will be signed and dated by the participant, their

parent/guardian and the researcher; a copy of the signed consent form will be then given to the participant and their parent/guardian. The original consent/assent form will be retained at the site in the Investigator Site File and a copy in the participant's medical records.

Where electronic consent/assent is used and the parent/guardian has an email address they are willing to provide, an electronic version of the signed ICF will be automatically emailed to them. If the parent/guardian agree, a copy of the consent/assent form may also be emailed to the participant. If the parent/guardian does not have/does not provide an email address the local team will be able to print a copy of the signed consent/assent form and provide this to the parent/guardian and participant. A copy of the electronic consent/assent form downloaded from the trial database should be placed in the Investigator Site File and a copy in the participant's medical record. Electronic tablets will be provided to each site to log onto the REDCap Data Management system to enter the data directly into the trial database.

- **Remote consent process**

Remote consent can be completed via a REDCap link or completion of a paper consent form/consultee declaration/assent form (as applicable) which will have been sent to the potential participant in the post with the relevant study invite letter and information leaflet(s).

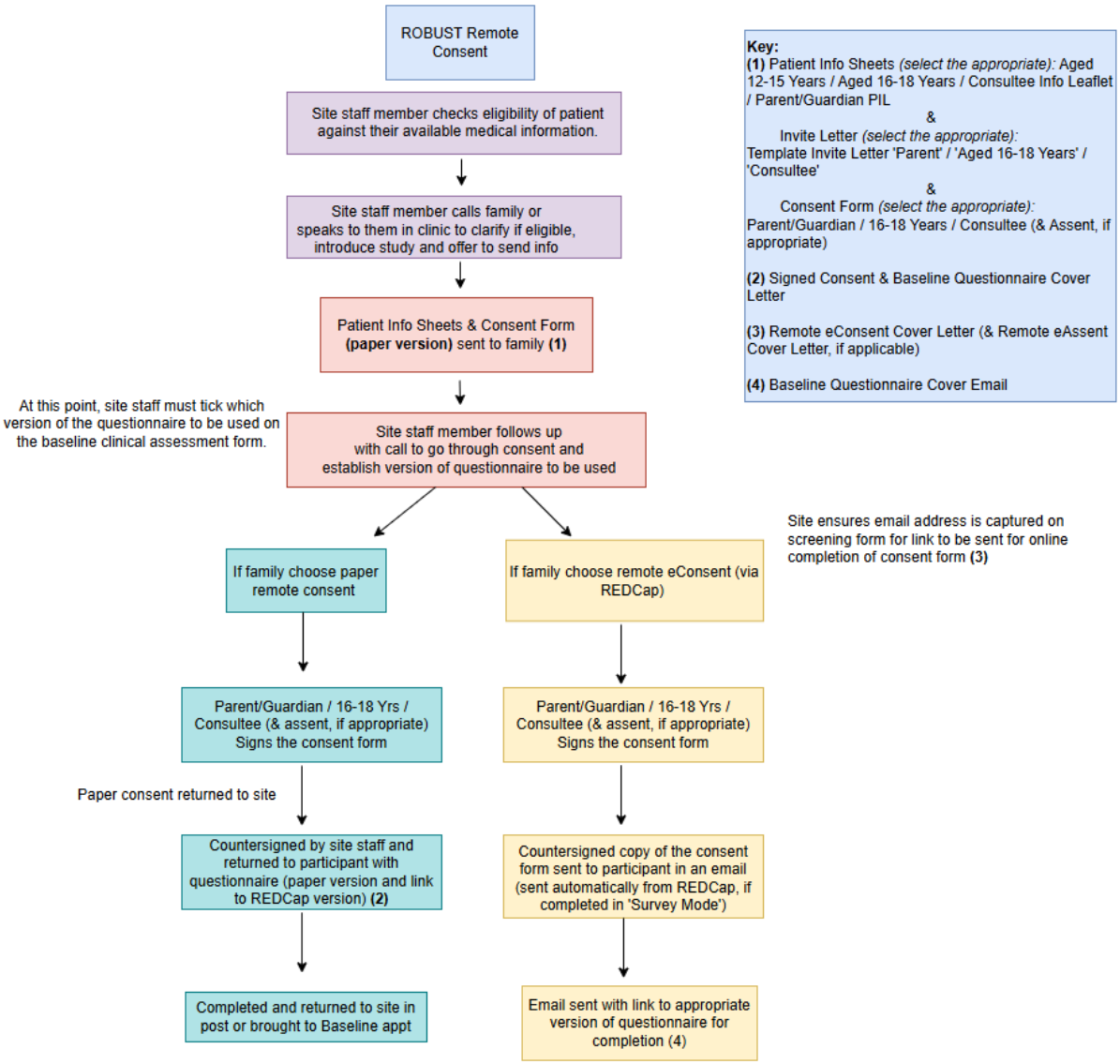
Remote eConsent (using REDCap) or remote completion of the paper consent form for participation in the trial may be obtained by the clinician/research staff member, following an initial contact, at site or via telephone. The remote eConsent will be obtained in accordance with OCTRU's standard operating procedure for obtaining consent.

Study information to introduce the study will have been provided following this initial contact by a letter/email using a standard template, to the patient and their parent/guardian/consultee (patients seen in clinic may have also obtained information during their visit).

Where remote consent will be used, potential participants will be asked to provide an e-mail address/postal address for receiving consent documents prior to obtaining written informed consent. The clinician/research staff member must allow sufficient time for the potential participant and their parent/guardian or consultee to consider the information sent to them, ask questions and have these answered satisfactorily. If happy to proceed, the patient and their parent/guardian/consultee will be sent a unique link via email to the electronic consent/consultee form and assent form for completion (unless they express a preference for completing the paper copy previously sent to them with the study information). The relevant site staff member will be required to countersign all consent forms completed remotely, in the same way as for paper forms, and verify the identity of the participant. If using REDCap, once completed, each form will be countersigned immediately by a member of the site research team authorised to do so. An electronic pdf copy will then be emailed automatically to the participant and parent/guardian or consultee (if applicable). If completing the paper copy, the participant/parent/consultee will need to return the countersigned informed consent form/consultee form (and assent form, if applicable) in the post to the site staff member to countersign. The countersigned copies will be sent to the participant and parent/guardian/consultee (as applicable) for their records.

The potential participant's (or parent/guardian/consultee) e-mail address will not be retained within any study systems once this e-mail has been sent, ensuring that patients who decide not to consent will not have their e-mail address retained by the central study team. The baseline questionnaire can be sent out for completion once consent is obtained, ahead of the initial appointment. An appointment will then be required to complete the baseline clinical assessment and randomisation. Please see Remote Consent Flowchart below for further details on this process.

**Remote Consent Flowchart:**




### 15.3 Optional aspects of consent

The participant/parent/guardian/consultee may agree to the retention of their contact details for up to five years to enable long term follow up. This is an optional aspect of the consent process. Participants and their parent/guardian/consultee may also choose to receive a summary of the results at the end of the trial.

### 15.4 Individuals lacking capacity to consent

Individuals lacking capacity to consent to trial participation will be eligible to enter the trial, following consent procedures outlined in Section 15.1. If the participant turns 16 during their participation in the trial and the PI confirms that the adolescent does not have capacity to consent for themselves, the parent/guardian will be asked to complete a Consultee Declaration Form (England and Wales) or a Legal Representative Consent Form (Scotland).

### 15.5 GP notification

Permission from the participant (and/or their parent/guardian) will also be obtained to inform their GP and their community physiotherapist service of their inclusion in the trial and their trial treatment allocation. An approved GP letter will be sent by the ROBUST central CTU team together with trial information to the participant's community physiotherapist service/ GP informing them of their participation in the trial.

### 15.6 Re-consenting

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent/assent will be obtained using an amended consent/assent form which will be signed by the participant (and/or their parent/guardian). Continuing consent will also be sought from those participants who reach their 16th birthday during the intervention period or during follow up who were originally consented into the trial by their parent or guardian. The local trial team will discuss and confirm with the PI whether the participant has capacity to consent for themselves to continuing participation. The PI and their local site team will be able to review the participant's medical record to facilitate this decision. If capacity to consent is confirmed the participant will be asked to consent during their next clinic visit. The consent form can be completed on REDCap or on paper and the clinician will be required to countersign. Alternatively, the site team may choose to send a letter inviting the young person to read the 16-18 Year Olds PIL and, if happy to do so, sign and return a Continuing Consent form to their local site (using a stamped addressed envelope). If the PI confirms that the adolescent does not have capacity to consent for themselves, the parent/guardian will be invited to complete a Consultee Declaration Form (for those in England and Wales) or a Legal Representative Consent Form (for those in Scotland). Alternatively, the site team may choose to send a letter inviting the parent/guardian to complete the confirmation of continued consent using the appropriate form listed above. A stamped addressed envelope will be enclosed to enable the return of the signed consent form to the local site.

## 16 RANDOMISATION

### 16.1 Timing of randomisation

Randomisation will take place once informed consent has been given, eligibility has been confirmed and baseline assessments have been made.

### 16.2 Randomisation procedure

Eligibility will be confirmed at randomisation. Participants will be randomised using the REDCap randomisation system, a centralised validated computer randomisation program, accessed within the ROBUST REDCap trial database. This will either be undertaken directly by the local research team at the site or by contacting the ROBUST Trial Office over the phone, which will access the system on their behalf, depending on the facilities available at the trial sites.

Participants will be randomised to one of the following treatment arms:

| Arm | Treatment |
|---|---|
| Strengthening intervention programme (intervention) | An individually tailored strengthening programme overseen by a physiotherapist via 6 one-to-one sessions over 16 weeks |
| Usual NHS care (control) | An assessment with a physiotherapist and NHS advice on self-management, including access to supporting information and continuation of any usual exercise, fitness/physical activity programme (as applicable). |

Upon randomisation of a participant the ROBUST trial office and a member of the site research team will be notified by an automated email.

### 16.3 Randomisation methodology

Consented participants will be individually randomised (1:1) to receive either the intervention or control arm.

Randomisation will be performed using a minimisation algorithm (or randomisation schedules) to ensure balance between the two treatment groups using the following stratification factors:

- Centre
- Sex
- Distribution (bilateral or unilateral CP)
- GMFCS level (levels I and II vs III)

The first few participants will be randomised using a simple randomisation schedule, prepared by the trial statistician, to seed the minimisation algorithm, and a non-deterministic probabilistic element will be included to prevent predictability of treatment allocation. The randomisation schedule will be designed by the OCTRU trial statistician and full details will be detailed in the Randomisation and Blinding Plan in the confidential statistical TMF.

#### 16.3.1 Justification for stratification factors

Stratification will be used to ensure equal allocation of subgroups of participants to the intervention and control arm across important baseline prognostic factors. Stratification factors include recruiting centre, sex, distribution (whether bilateral or unilateral CP) and GMFCS level (levels I and II vs. III) as children with higher levels of disability present differently and thus likely to have different outcomes to those children with lower levels of disability.

### 16.4 Back-up randomisation procedure

An emergency randomisation (back-up) list will not be available as randomisation is not time critical.

## 17 TRIAL ASSESSMENTS/PROCEDURES

The trial flow chart can be found in APPENDIX 1 –TRIAL FLOW CHART of this protocol.

### 17.1 Overview

Table 2 shows scheduled assessments for the trial.

**Table 2. Scheduled assessments/participant timeline**

| **TIME POINT (from randomisation)** | Pre randomisation | Baseline | 0-4 months | 6-month follow up | 12-month follow up |
|---|---|---|---|---|---|
| **ENROLMENT:** | | | | | |
| Screening log | ✓ | | | | |
| Eligibility confirmed | ✓ | | | | |
| Informed consent | ✓ | | | | |
| Randomisation | | ✓ | | | |
| **INTERVENTIONS:** | | | | | |
| Progressive resistance exercise programme (if randomised to) | | | ✓* | | |
| NHS usual care (if randomised to) | | | ✓* | | |
| **ASSESSMENTS:** | | | | | |
| Baseline demographic questionnaire | ✓ | | | | |
| Clinician/research staff assessed outcomes (joint range of motion & motor function) | ✓* | | | ✓* | |
| Participant assessed outcomes (questionnaire) | ✓ | | | ✓ | ✓ |
| Follow-up reminders | | | | ✓ | ✓ |

*denotes time points that require clinic/hospital attendance, but other assessments at this time points could be undertaken electronically/over the telephone'.

### 17.2 Trial questionnaires

Where possible, questionnaires will be completed electronically by the participant and/or their parent/guardian. The parent/guardian will be e-mailed a link to complete the trial questionnaires. Where the parent/guardian gives permission, a copy will also be sent to the participant. Participants and/or their parent/guardian will be asked as part of their baseline assessment whether they wish to complete follow-up questionnaires electronically or on paper with postal return. Any links sent to a participant by email to a questionnaire are unique to a participant and their timepoint/questionnaire in the trial. Paper questionnaires may also be used if requested. If a paper-based version of the electronic questionnaire is requested, this will be sent to participants and their parent/guardian to complete and return to the Trial Office in a prepaid envelope.

### 17.3 Data Collection

Table 3 provides a summary of time points at which trial outcomes will be assessed.

**Table 3: Time points at which outcomes will be assessed**

| Outcome | Measurement | Time point |
|---|---|---|
| Demographic | Age, Sex, Height, Weight, Ethnicity, Distribution (bilateral or unilateral CP), GMFCS level (Levels I, II or III), Orthotic wear, Neurological pattern, epilepsy or visual impairment | 0 |
| Primary | | |
| Functional mobility | Gait Outcomes Assessment List (GOAL) questionnaire (23). | 0, 6 month |
| Secondary | | |
| Functional mobility | Gait Outcomes Assessment List (GOAL) questionnaire (23). | 0, 12 month |
| Muscle Strength (clinician assessed) | Five-time sit-to-stand test for adolescents with CP (24) | 0, 6 month |
| Motor Function (clinician assessed) | Timed up and Go test (25) TUG | 0, 6 month |
| Independence | GOAL subdomain A (23) | 0, 6, 12 month |
| Balance | GOAL subdomains A,B,D (23) | 0, 6, 12 month |
| Pain and discomfort | GOAL subdomain C (23) | 0, 6, 12 month |
| Health-related quality of life | EQ-5D-Y (26) | 0, 6, 12 month |
| Educational outcomes | Educational attendance record (days missed) | 0, 6, 12 month |
| Exercise adherence | Patient/Parent self-reported adherence | 6, 12 month |
| Additional physiotherapy treatment | Patient/Parent self-reported | 6, 12 months |

#### 17.3.1 Baseline data collection

After the participants have been assessed for eligibility and informed consent has been obtained, participants with the support of their parent/guardian will be asked to complete the baseline assessment questionnaire that will record simple demographic information (Table 3) and baseline measurements for the primary and secondary outcomes. The participants will complete the baseline questionnaire electronically, using tablets provided to each site (or via a link received in an email, if applicable), and before learning the outcome of the randomisation. The questionnaire will also be available in paper format if required. The family's ability to access the internet will be assessed as part

of the participant's baseline assessment. If required, a tablet computer will be sent directly to the family from the Trial Office for participants randomised to the strengthening intervention programme (if applicable).

Clinician assessed outcomes (i.e. muscle strength and motor function) at baseline will be recorded electronically by a physiotherapist/research staff member at site and before learning the outcome of the randomisation.

### 17.3.2 Follow-up data collection

Detail of the outcomes to be assessed, how they will be measured and at which time points are shown in Table 3. Patient-reported will be assessed using an electronic (online) questionnaire at 6 and 12 months from initial randomization. If requested a paper-based version of the electronic questionnaire will be provided. The questionnaire will be thoroughly tested prior to the trial to minimize the chance of misunderstanding, misinterpretation and missing data.

At 6 and 12 months participants and/or their parent/guardian will be sent an email with a personalised link asking them to complete the electronic questionnaire. For those who do not respond to the initial follow up questionnaire a reminder email will be sent 2 weeks later. If a paper-based version of the electronic questionnaire is requested, this will be sent to participants and their parent/guardian to complete and return to the Trial Office in a prepaid envelope. This data would be entered onto the trial database by the data entry personnel at the Trial Office. For those who do not respond to the initial postal questionnaire a postal reminder will be sent 2 weeks later. Telephone and email follow-up will be used (2 weeks later), as applicable, to contact those who do not respond to either the initial or reminder questionnaire. Telephone and email follow-up will also be used to collect a core set of questionnaire items for the Gait Outcomes Assessment List (GOAL) questionnaire (primary outcome), and other outcome data, if these have not been fully completed on the returned questionnaire.

Clinician assessed outcomes will be assessed at a face to face clinic appointment at 6 months by a blinded physiotherapist/research staff member who is blind to the treatment allocation and has not been involved in delivery of the intervention or usual care. Participants who do not attend this face-to-face clinic appointment will be contacted by phone by the local site team and a new clinic appointment sent. The 6-month time point for muscle strength has been chosen to minimise participant burden and is in line with the 6-month primary outcome, improvement in functional mobility (measured using the GOAL questionnaire). At the 6 month clinic appointment participants and their parent/guardian will be asked if they have completed their 6 month follow up questionnaire. If they have not yet completed the questionnaire they will be asked to complete this as part of their clinic appointment.

## 17.4 Withdrawal

Withdrawal of consent means that a participant (and/or their parent/guardian) has expressed a wish to withdraw from the trial altogether or from certain aspects of the trial only. The type of withdrawal will be collected on the CRF labelled 'Withdrawal'.

Participants may also be withdrawn from the trial (or aspects of the trial) by their clinician if they believe the participant needs to be withdrawn.

The Withdrawal CRF should be completed to document the reasons for withdrawal and state who the decision to withdraw was made by. Discussions and decisions regarding withdrawal should be documented in the participant's medical notes. Investigators should continue to follow- up any Serious Adverse Events (SAEs) and should continue to report any SAEs to resolution in the CRF in accordance with the safety reporting section.

Where a participant expresses a wish to withdraw from the trial, the trial team will determine which aspect(s) of the trial the participant wishes to withdraw from.

The aspects of the trial that the participant and their parent/guardian may request to withdraw from are as follows:

- No longer willing to receive trial intervention
- No longer willing to complete trial questionnaires
- No longer willing to attend trial visits
- No longer willing to be contacted by the research team to obtain CRF/outcome data
- No longer willing for routine data from Health data providers e.g. NHS England / Digital Health and Social Care Scotland to be provided to the trial

Where a participant and/or their parent/guardian wishes to withdraw from all aspects of trial participation detailed above this will be recorded on the Withdrawal CRF as full withdrawal.

In addition to participant self-withdrawal, an investigator may decide to withdraw a participant from trial treatment for clinical reasons. Participants and their parent/guardian will still be asked to participate in the collection of follow-up data. The reason for withdrawal will be recorded on the trial withdrawal case report form. Withdrawn participants will not be replaced as we have allowed for possible withdrawals and loss to follow-up in the estimated sample size.

Completion of the Withdrawal CRF by the site research team will trigger a notification to the Trial Office. Appropriate action will be taken by the trial teams (centrally at the trial office (CTU) and by the site research team at each participating site) to ensure compliance with the participant's withdrawal request. This may include marking future CRFs as not applicable and ensuring any relevant communications which the participant had consented to receive regarding their participation are no longer sent.

Data collected up to the point of withdrawal will be used in the trial analysis as explained in the PIS, unless the participant specifically requests otherwise.

### 17.5 Communication with trial participants by the central trial team

Participants and their parent/guardian will be notified to complete trial questionnaires by e-mail, or where they have selected to receive postal questionnaires these will be posted to the participant and their parent/guardian. Participants and their parent/guardian will receive an initial e-mail and a reminder two weeks later. Participants that do not complete their trial questionnaires will be telephoned by a member of the central trial team to collect outcome data.

## 18 BLINDING AND CODE-BREAKING

### 18.1 Blinding

Table 4 provides an overview of the blinding status of all individuals involved in the conduct and management of the trial.

**Table 4: Blinding status of those involved in trial conduct and management**

| Role in trial | Blinding status | Additional information |
|---|---|---|
| Participants | Not blinded | It is not possible to blind due to nature of the intervention. Participants will be told their treatment allocation at their initial appointment. |

| | | |
|---|---|---|
| Physiotherapists delivering intervention | Not blinded | Physiotherapists delivering the intervention cannot be blinded to the randomisation allocation. |
| Physiotherapists/research staffperforming outcome assessments | Blinded, where possible | The secondary outcome of muscle strength and motor function (measured using the five-time sit-to-stand test for adolescents with CP (24) and Timed up and Go test (25)) will be assessed by a blinded physiotherapist at site who has not been involved in delivery of the intervention or usual care, where possible. |
| Physiotherapists conducting monitoring visits | Not blinded | It is not possible to blind physiotherapists conducting monitoring visits. |
| Data entry personnel | Not blinded | It is not possible to blind staff entering trial data. |
| Site research staff including Principal Investigator (excluding physiotherapists/research staffas detailed above) | Not blinded | Not possible due to the nature of the intervention. Following randomisation, an email will be sent to the PI (unblinded for participants they randomise only) and/or member of the site research team performing the randomisation (as delegated) confirming treatment allocation. |
| Chief Investigator | Blinded for those at sites other than their own, except for any SAE causality assessment | The Chief investigator will remain blinded to treatment allocation overall (knowledge of treatment allocation is limited to participants at their own site). In instances where serious adverse events are reported, the CIs will become unblinded to complete the full causality assessment. |
| Database programmer | Not blinded | The database programmer is responsible for the management of REDCap randomisation system and the REDCAP database and will have access to all unblinded datasets within both systems. |
| Trial Management staff within SITU. | Not blinded | Trial Management staff within SITU will remain blinded to treatment allocations as far as possible; there may be situations where site staff require support for randomisation and in these situations, it is acknowledged that trial management staff may become aware of treatment allocation but efforts will be made to ensure the blind where possible. Serious Adverse Event reports will be handled by the trial management team who may become unblinded to a participant's treatment allocation. |
| Data Management | Not blinded | Data management staff will have access to the unblinded datasets within the trial randomisation system and database to ensure data quality and undertake central monitoring activities. |
| Trial statistician and Senior Trial Statistician | Not blinded | The trial statistician and senior trial statisticians will have access to treatment allocations or data needed for generating the Data and Safety Monitoring Committee (DSMC) closed reports and the final analysis. |

### 18.2 Code break/ unblinding

Not applicable for this trial.

## 19 SAMPLES

No new or existing samples will be taken/used in the ROBUST trial.

## 20 SAFETY REPORTING

### 20.1 Safety reporting period

Safety reporting for each participant will begin from the time of consent and will end when participant has reached their final main follow-up time point, at 12 months post-randomisation. Serious adverse events will be recorded at any time point during the safety reporting period.

### 20.2 Definitions

| | |
|---|---|
| Adverse Event (AE) | Any untoward occurrence in a clinical trial participant. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporarily associated with the trial procedures, whether or not considered related to the procedures. |
| Serious Adverse Event (SAE) | Any AE that:<br>• results in death<br>• is life-threatening[1]<br>• requires hospitalisation or prolongation of existing hospitalisation<br>• results in persistent or significant disability or incapacity<br>• is a congenital anomaly or birth defect; or<br>• is otherwise considered medically significant by the Investigator[2] |
| Unexpected Serious Adverse Event | This is a term used to describe a serious adverse event related to the trial (i.e. resulted from administration of any of the research procedures) and is unexpected (not listed in the protocol as an expected occurrence). |

[1] participant 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.

[2] Medical events that may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

### 20.3 Expected adverse events

Expected general side effects of any form of exercise, such as delayed onset muscle soreness and temporary increases in pain (<7 days) will not be recorded as adverse events. This is based on our experience from the STAR trial (19), where exercise related pain was reported as adverse event and this led to over-reporting.

The participants and their parent/guardian will be asked to notify the treating therapist or GP, as would occur during normal practice, if they suspect that they are suffering an adverse effect. We consider it unlikely that tendon/muscle rupture will occur as a result of the intervention, although

there is a theoretical risk of exceeding the capacity of the muscle/tendon with stretching. Therefore, any admission for pain management or surgery to address tendon or muscle injury would not represent a Serious Adverse Event (SAE). The intervention has been designed to introduce a gradual increase in strength, thus minimising the risk of musculoskeletal injury. A list of anticipated symptoms and potential AEs and SAEs is presented in Table 5:

**Table 5: Anticipated AEs and SAEs related to the intervention**

| Anticipated symptoms not requiring reporting | AEs | SAEs |
|---|---|---|
| Delayed onset muscle soreness lasting less than 7 days | Muscle soreness persisting for more than 7 days after performing the exercises | Significant cardiovascular event occurring during exercise (for example: fainting episodes related to hypotension or cardiac arrhythmia). |
| Mild and transient (less than 7 days) alteration in walking pattern (limping) | Acute onset of significant pain during the exercise intervention | |
| | Deterioration of walking pattern (limping) for more than 7 days | |
| | Bone fracture,<br>Joint minor injury, swelling or inflammation,<br>Significant joint injury requiring admission to hospital and/or surgical treatment | |
| | Vaso-vagal episode (fainting) during the intervention exercise | |

### 20.4 Procedures for recording adverse events

The potential occurrence of adverse events related to the intervention as outlined in Table 5 will collected on an adverse event form. Participants and their parent/guardian will be provided with information on the potential adverse events resulting from exercise as part of their treatment, including what they should do if they experience an adverse event, as would happen as part of standard NHS procedures. The participants and their parent/guardian will be asked to notify the treating therapist, as would occur during normal practice, if they suspect that they are suffering an adverse effect. In addition, at the 6-month clinical follow-up visit the participants and their parent/guardian will be asked if they have experienced any adverse events. At the end of the participant's 12-month follow-up period it will be confirmed with trial teams whether any further adverse events were reported. The participants' treating physiotherapist will be notified by the Trial Office of any anticipated adverse events which require any further reporting, as defined in Table 5.

### 20.5 Relatedness/causality

The assessment of "relatedness" to the trial intervention is the responsibility of the site investigator at site or an agreed designee according to the following definitions:

| Relationship to intervention | Attribution (causality) | Description |
|---|---|---|
| **Unrelated** | Unrelated | The AE is clearly NOT related to the intervention |
| | Unlikely | The AE is doubtfully related to the intervention |
| **Related** | Possible | The AE may be related to the intervention |
| | Probable | The AE is likely related to the intervention |
| | Definite | The AE is clearly related to the intervention |

### 20.6 Reporting of SAEs from sites to the CTU study team

SAEs are likely to be very rare and are highly unlikely to occur as a result of either the exercise therapy delivered in this trial. Only serious adverse events considered by the site investigator to be related (possibly, probably, or definitely) to the trial intervention (as defined in Table 5) will be reported immediately to the central trial team. Such events will be reported immediately to the trial office as follows:

SAEs will be reported by the site research team using the SAE form within the REDCap study database within 24 hours of becoming aware of the event. The CTU is automatically notified of the SAE report through the database. A paper SAE form should be used as a back-up if the SAE form is not available electronically. This should be e-mailed to robust@ndorms.ox.ac.uk within 24 hours of becoming aware of the event. The central CTU study team will acknowledge receipt of any SAEs reported via e-mail within one working day and provide the site with a unique SAE Log number.

The site principal investigator will make a full assessment of causality and expectedness of the SAE. The Chief Investigator/nominated person (who is an appropriately qualified and trained individual) will then centrally review any reported SAEs and perform the assessment of expectedness on behalf of the Sponsor and will:

- assess the event for seriousness, expectedness and relatedness to the trial intervention;
- take appropriate medical action, which may include halting the trial and inform the Sponsor of such action;
- if the event is deemed related to the trial intervention shall inform the REC using the reporting form found on the HRA web page within 15 days of knowledge of the event;
- send any follow-up information and reports to the REC;
- make any amendments as required to the trial protocol and inform the REC as required

The Chief Investigator will be informed immediately of any serious adverse events and assess the information in conjunction with any treating medical practitioners and confirm causality and expectedness. If in doubt, the CI will raise queries with the treating medical practitioner the site.

All intervention related serious adverse events will be recorded and reported to the REC as part of the annual reports. Unexpected serious adverse events related to the intervention/trial procedures will be reported within the timeframes to the REC as stated below. The central trial team will be responsible for all adverse event reporting.

Any participant who experiences a serious adverse event may be withdrawn from the trial at the discretion of the site principal investigator. The participants' GP will be notified by the Trial Office of any anticipated serious adverse events, as defined in Table 5.

### 20.7 Reporting procedure for unexpected serious adverse events

Any SAEs that are considered by the reporting Investigator or the Nominated Person to be related (i.e. resulted from administration of any of the research procedures) and unexpected (that is, the type of event is not listed in the protocol/reference documented as an expected occurrence of the trial intervention) will be submitted to the REC within 15 days after becoming aware of the event.

## 21 PREGNANCY

Whilst unlikely to occur, uncomplicated pregnancy will not be classed as a contraindication to continuation with the intervention. For complicated pregnancy, continuation of the intervention will be individually assessed based on the treating physiotherapist's judgement.

## 22 STATISTICAL CONSIDERATIONS

### 22.1 Statistical Analysis Plan (SAP)

The statistical aspects of the trial are summarised here with details fully described in a statistical analysis plan (SAP) that will be drafted early in the trial and finalised prior to the final analysis data lock, or any planned interim comparative analyses. The SAP will be written by the Trial Statistician in accordance with the current OCTRU SOPs. The TSC and DSMC will review and, if necessary, provide input on the SAP. Any changes or deviations from the original SAP will be described and justified in any protocol amendments, final report and/or publications, as appropriate.

### 22.2 Sample Size/Power calculations

The target sample size for the trial is 334 randomised participants (167 in each treatment arm) (Power Analysis and Sample Size (PASS) 13, www.ncss.com). This will allow detection of a clinically meaningful moderate standardised effect size of 0.4 with a two-sided 5% significance level, 90% power, and allowing for 20% loss to follow-up. The standardised effect size of 0.4 corresponds to a difference of 6.8 points on the GOAL outcome measure (23), which ranges from 0-100, with a standard deviation of 17. A difference of 6.8 is considered functionally important and achievable by key stakeholders, including patients who provided input in focus groups, and clinicians we surveyed in preparation for the application. Standard deviations of this magnitude have been reported in similar patient populations (23, 43). It is anticipated that the DSMC will review the sample size assumptions after approximately 50% of the participants have been recruited.

### 22.3 Description of Statistical Methods

Results will be reported in line with the CONSORT statement and will be described fully in a separate SAP. Summary descriptive statistics will be used to describe the baseline characteristics by treatment group using means with standard deviations or medians with interquartile ranges as appropriate for continuous variables and counts with percentages for binary or categorical variables. A single final unblinded statistical analysis will take place after all follow-up has been completed, and sufficient time has been allowed for data collection and cleaning. No formal interim statistical analyses are planned or have been allowed for in the trial design.

It is anticipated that all statistical analysis will be undertaken using Stata (StataCorp LP, www.stata.com) or other well-validated statistical packages.

The primary analysis will use the randomised ("intention-to-treat (ITT)") population, analysing participants with available outcome data in their randomised groups, regardless of adherence to their allocated intervention. Primary and secondary outcome analyses will use two-sided 5% significance and 95% confidence intervals with associated p-values reported throughout.

### 22.4 Primary Outcome

The primary objective of the statistical analysis is to identify if the two treatments under investigation lead to a difference in observed GOAL score at 6-months post randomisation.

Data for the GOAL score will be presented descriptively at baseline, 6 and 12 months post randomisation. Differences in GOAL scores between the trial arms will be estimated using a multi-level mixed effects regression model, allowing for repeated measures clustered within participants. The model will be adjusted for stratification factors (sex (male, female), distribution (bilateral or unilateral CP) and GMFCS level (levels I and II vs III)) and other important prognostic factors (i.e. neurological pattern, epilepsy or visual impairment), including the baseline GOAL scores. The use of robust standard errors will account for potential clustering within randomising sites. A treatment by time point interaction (used as categorical) will be included, indicating the protocol stipulated follow-up time point to which the assessment refers. Model diagnostics, including approximate normality of the residuals, will be assessed. Adjusted mean differences and unadjusted mean differences between the groups will be presented together with 95% confidence intervals (CIs) and p-values, with focus on the treatment effect at 6 months, i.e. the primary follow-up time point.

We will explore the effect of non-adherence with the randomised interventions using complier-average causal effects (CACE) analyses. Adherence will be defined as having completed all 6 physiotherapy sessions, or the participant having completed treatment as defined by their treating physiotherapist.

### 22.5 Secondary outcome(s)

Secondary outcomes will be analysed using generalised linear models, with model adjustment as described for the primary analysis above.

In addition to the analysis of the secondary outcomes, the number of AEs and SAEs will also be analysed by treatment arm. The proportion of participants with at least one SAE will be compared. Details of the events, including expectedness and relatedness of the SAEs will be presented, together with information on the timing of the events.

### 22.6 Inclusion in analysis

The primary and secondary analyses will be performed on the ITT population, analysing participants with available outcome data in their randomised groups, regardless of adherence.

### 22.7 Subgroup analysis

We will explore consistency of the primary treatment effect for important diagnostic subgroups. We will confirm the final subgroups in the SAP, but as a minimum, these will include stratification factors (sex, distribution (bilateral or unilateral CP) and GMFCS level (levels I & II vs III)), and categories for baseline GOAL scores. Subgroup effects will be obtained from linear regression models for the 6-month primary outcome, adjusted in line with the above model specifications, and an interaction between randomised treatment and subgroup. Results will be displayed and viewed as exploratory.

### 22.8 Interim analyses

The main outcomes will be analysed as stated in the SAP once the trial follow-up has been completed. There are no plans for carrying out any formal interim analysis of the main outcomes of the trial. We considered using an early stopping rule, but rejected this idea as the treatment period is extensive and there is no strong link demonstrated between early response and later outcomes.

### 22.9 Stopping rules

As no formal interim analyses are planned, no stopping rules have been incorporated into the trial design. An independent DSMC will review the accumulating data at regular intervals and may

recommend pausing or stopping the trial in the event of safety concerns, as specified in the DSMC Charter. The TSC will make any final decision to terminate the trial if appropriate.

### 22.10 Procedure for accounting for missing data

Missing data will be reported and summarised by treatment arm. A multi-level mixed effects regression model will be used to analyse all available data for the primary outcome, and includes all participants with at least one available follow-up assessment. In this analysis approach, unavailable observations either due to missed visits or to a participant leaving the trial prematurely are assumed to be similar to observed outcomes from similar participants at the same time points (missing at random [MAR]). We do not anticipate using multiple imputation for missing outcome data in the analysis, as the multi-level mixed effects regression model including all participants with follow-up data at either 6 or 12 months, and adjusted for randomisation factors and important prognostic factors is expected to produce unbiased results under a MAR mechanism (44). Multiple imputation also assumes a missing at random mechanism, and is therefore not expected to add value to the primary analysis model.

The potential impact of informative missing data (missing not at random) on the treatment effect in the GOAL at 6 months will be investigated. Specifically, participants with missing data will be assumed to have outcomes up to 6.8 points worse than those with observed outcomes, using Stata's 'rctmiss' command or similar approaches.

### 22.11 Procedures for reporting any deviation(s) from the original statistical analysis plan

Any deviation(s) from the original SAP will be described in the final statistical report.

### 22.12 Internal pilot/Decision Points

An internal pilot will progress seamlessly to the definitive trial if predefined progression criteria regarding recruitment are reached. The internal pilot trial will mirror the procedures and logistics undertaken in the main definitive trial. Data from the internal pilot trial will contribute to the final analysis. The purpose of the internal pilot is to test and refine the recruitment process and explore treatment acceptability. We will collect data on the number of patients screened, assessed for eligibility and randomised to determine the feasibility of the main trial. The decision to progress to the main trial will be made in collaboration with the TSC and NIHR HTA programme based on pre-defined progression criteria. Progression to the main trial, will be informed using the traffic light system recommended by Avery (45) in terms of the decision-making process for stopping (red), amending the trial (amber) or proceeding (green) to a main trial. We will include a formal assessment of treatment delivery to monitor adherence as part of the internal pilot. Participants allocated to the usual care group will not have access to the specific strengthening programme of the intervention group. We will also monitor intervention fidelity during the intervention pilot as part of our site monitoring visits. Treatment compliance and retention (using information obtained from participant's physiotherapy session treatment logs) will be assessed to inform the main trial. The internal pilot will also identify how well the sites are able to accommodate the delivery of our interventions within their existing workloads.

Stop-go criteria will be reviewed after 6 months of recruitment.

Stop-go criteria for the pilot phase are given in table 6 together with the definitions of how each will be measured. The total number of participants recruited is the main criteria. The figures in Table 6 are based on the overall calculation of recruiting 2-3 cases per month per site.

**Table 6: Stop-go criteria for internal pilot phase**

| Progression criteria | Red | Amber | Green |
|---|---|---|---|
| Total number of participants recruited | <26 | 26-51 | ≥52 |
| Trial recruitment % complete | <50% | 50-≤99% | 100% |
| Recruitment rate/ site / month | <1 | 1-2 | >2 |
| Number of sites open | <3 | 3-5 | 6 |

The internal pilot trial will mirror the procedures and logistics undertaken in the main definitive trial. It is intended that the trial will progress seamlessly into the main phase, with internal pilot participants included in the final analysis.

## 23 HEALTH ECONOMICS

There are no health economic analyses to be undertaken as part of the trial.

## 24 DATA MANAGEMENT

The data management aspects of the trial are summarised here with details fully described in the trial-specific Data Management Plan (DMP). See section 24.6 'Data Recording and Record Keeping for information on management of personal data.

### 24.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no prior written or electronic record of data).

The following data are expected to be recorded directly on the CRFs hence are to be considered source documents for this trial:

- All participant completed questionnaires.
- Clinical assessed 5 time sit-to-stand test for adolescents with CP and Timed up and Go test

### 24.2 Location of source data

The location of source data in the trial is listed with the tables within section 0.

### 24.3 Case report forms (CRFs)

The Investigator and trial site staff will ensure that data collected on each participant is recorded in the CRF as accurately and completely as possible. Details of all protocol evaluations and investigations must be recorded in the participant's medical record for extraction onto the CRF. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the CRFs from the relevant source data held in the site medical record(s).

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

### 24.4 Non-CRF data

All trial data will be recorded on the CRF. No additional data will be held outside of the CRF.

### 24.5 Access to Data

To ensure compliance with regulations, direct access will be granted to authorised representatives from the Sponsor and host institution to permit trial-related monitoring, audits and inspections. The

data submitted by trial participants directly via the trial database (i.e. electronic patient reported outcomes) will also be made available to the participating site that recruited the participants; this is detailed within the PIL so that participants and their parent/guardian are aware of who will have access to this data.

Members of the trial team will only be able to access data that they need to, based on their roles and responsibilities within the trial.

### 24.6 Data Recording and Record Keeping

The case report forms will be designed by members of the trial management team which will include the Chief Investigator, trial statistician(s) and trial manager.

Data will, wherever possible, be collected in electronic format with direct entry onto the trial database by site staff or participants. Electronic data collection has the major advantage of building "data logic" into forms, minimising missing data, data input errors and ensuring the completeness of consent and assent forms. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Sites will be provided with an electronic tablet to use for data collection. If the site or participant and their parent/guardian, as applicable, are not able to complete the CRFs electronically (due to poor internet connection), paper-based CRFs will be available in the Investigator Site File, these will be returned to the Trial Office in Oxford via post using a pre-addressed stamped envelope, email as appropriate, or via Trial Office staff at site visits. Participant data will be stored and transported in accordance with OCTRU SOPs.

All data entered will be encrypted in transit between the client and server. All electronic patient-identifiable information, including electronic consent forms, will be held on a server located in an access-controlled server room at the University of Oxford. The data will be entered into a GCP compliant data collection system and stored in a database on the secure server, accessible only to members of the research team based on their role within the trial. The database and server are backed up to a secure location on a regular basis.

Personal identifiable data will be kept separately from the outcome data obtained from/about the patients. Patients will be identified by a trial ID only.

Direct access to source data/documents will be required for trial-related monitoring and/or audit by the Sponsor, NHS Trust/Board or regulatory authorities as required.

Refer to section 28.5 for details about retention of participant identifiable data.

Data on paper forms or captured during phone calls to participants will be entered into the trial database by suitably trained central office staff. Full details of this process will be recorded in the DMP. The participants will be identified by a unique trial specific number in any data extract. Identifiable data will only be accessible by members of the trial team with a demonstrated need (managed via access controls within the application) and any additional processing of this will only be for the purposes of communication with the participant (e.g., sending follow-up reminders for follow up questionnaire completion or telephone follow-up).

### 24.7 Electronic transfer of data

Any electronic transfer of data during the course of the trial will be strictly controlled in accordance with the Oxford Clinical Trial Research Unit's (OCTRU) Standard Operating Procedure for Secure Information/Data Transfer.

## 25 QUALITY ASSURANCE PROCEDURES

A rigorous programme of quality control will be implemented to ensure protocol and intervention fidelity (i.e. the exercises being undertaken according to the protocol). The trial management group will be responsible for ensuring adherence to the trial protocol at the trial sites, and the trial team will observe treatment sessions for therapists. Quality assurance (QA) checks will be undertaken by OCTRU to ensure integrity of randomisation, trial entry procedures and data collection. The OCTRU has a QA team who will monitor this trial by conducting audits (at least once in the lifetime of the trial, more if deemed necessary) of the Trial Master File. Furthermore, the processes of obtaining consent, randomisation, registration, provision of information and provision of treatment will be monitored by the central CTU trial team. Additionally, the trial may be monitored, or audited by sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

A trial-specific data management and monitoring plan will be in place prior to the start of the trial.

### 25.1 Risk Assessment

This protocol is designed to deliver a risk-adapted approach to conducting the research. A risk assessment has been conducted and a monitoring plan will be prepared before the trial opens. The known and potential risks and benefits to participants have been assessed in comparison to those of standard of care. A risk management strategy is in place and will be reviewed and updated as necessary throughout the trial or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

### 25.2 Trial monitoring

Regular monitoring will be performed by the central CTU trial team according to a trial-specific monitoring plan. Data will be evaluated for compliance with the protocol, completeness and accuracy. The investigator and institutions involved in the trial will permit trial-related monitoring and provide direct on-site access to all trial records and facilities if required. They will provide adequate time and space for the completion of monitoring activities.

Trial sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness and timing. The case report form data will be validated using appropriate set criteria, range and verification checks. The trial site must resolve all data queries in a timely manner (within no more than 7 working days of the data query unless otherwise specified). All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the trial site for resolution.

Trial sites will also be monitored remotely and/or by site visit, as necessary, to ensure their proper conduct of the trial. Trial Office staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have. Any monitoring reports/data discrepancies will be sent to the site in accordance with OCTRU SOPs and the trial monitoring plan. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance, within 28 days as a minimum, or sooner if the monitoring report requests.

### 25.3 Audit and regulatory inspection

All aspects of the trial conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. Such audits or inspections may occur at any time during or after the completion of the trial. Investigators and their host Institution(s) should understand that it is necessary to allow auditors/inspectors direct access to all relevant documents, trial facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit. Anyone receiving notification of a Regulatory Inspection or audit that will (or is likely to) involve this trial must inform the Trial Office without delay.

### 25.4 Trial committees

#### 25.4.1 Trial Management Group (TMG)

A Trial Management Group (TMG) has been established, consisting of the core trial team, Chief Investigator and co-applicants. The TMG will be responsible for the day-to-day running of the trial and will meet monthly to report on progress and ensure milestones are met. A trial manager will oversee all aspects of the day-to-day trial management. The trial will be managed by a team at the Oxford Clinical Trials Research Unit.

#### 25.4.2 Data and Safety Monitoring Committee (DSMC)

A Data Safety and Monitoring Committee (DSMC) will be appointed to safeguard the interests of the trial participants to assess the safety and efficacy of the interventions during the trial, and to monitor the overall conduct of the trial, protecting its validity and credibility. The DSMC will be independent of the trial investigators and Sponsor and will adopt a DAMOCLES charter that defines its terms of reference and operation in relation to oversight of the trial. It will meet at least every 12 months over the duration of the trial. The independent DSMC will meet early in the trial to agree the terms of reference and to review confidential interim analyses of accumulating data. The DSMC will not be asked to perform any formal interim analyses of effectiveness. It will, however, review accruing data and summaries of that data presented by treatment group and will assess the screening algorithm against the eligibility criteria. It will also consider emerging evidence from other related trials or research and review any related SAEs that have been reported. The DSMC may advise the chair of the Trial Steering Committee at any time if, in its view, the trial should be stopped for ethical reasons, including concerns about participant safety or clear evidence of the effectiveness of one of the treatments. The DSMC will comprise an independent medically qualified clinician, specialist physiotherapist, statistician, and health service researcher.

#### 25.4.3 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be appointed and will meet at least annually over the duration of the trial. The TSC will monitor the trial's progress and will provide independent advice. The TSC will comprise independent clinicians, specialist physiotherapists, statisticians, health service researchers and patient representatives.

## 26 IDENTIFICATION AND MANAGEMENT OF PARTICIPATING SITES

### 26.1 Identification of recruitment sites

Recruitment sites will be selected based on suitability to conduct the trial. Potential sites will be invited to complete a site feasibility questionnaire (SFQ) which will be used by the Trial Management Group/Coordinating Centre to assess suitability of the site for the trial; the suitability assessment will primarily be based on the resources available at site and the feasibility of meeting recruitment targets.

Sites will be chosen so they reflect a range of settings (urban and rural) and are able to deliver the trial interventions. The local site principal investigator will be responsible for the conduct of the research

at their site. The site principal investigator will identify the staff responsible for the conduct of the trial and ensure that the trial roles and responsibilities are assigned in writing using the trial delegation log. They will also help with local queries and trial promotion. All potential sites will be screened with a site feasibility questionnaire to ensure they have sufficient potential participants and the clinical expertise and capacity to provide the treatments and manage the patients.

### 26.2 Trial site responsibilities

The Principal Investigator (the PI or lead clinician for the trial site) has overall responsibility for the conduct of the trial, but may delegate responsibility where appropriate to suitably experienced and trained members of the trial site team. All members of the trial site team must complete delegation log provided by the central trial team prior to undertaking any trial duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

### 26.3 Trial site set up and activation

The Principal Investigator leading the participating trial site is responsible for providing all required core documentation. Mandatory Site Training which is organised by the trial office (see below) must be completed before the site can be activated. Training in the trial processes will be administered at site initiation visits delivered either in person or online by the central CTU trial team. The Trial Office will check to confirm that the site has all the required trial information/documentation and is ready to recruit. The site will then be notified once they are activated on the trial database and are able to begin recruiting participants.

### 26.4 Training

Training in the trial processes will be administered at site initiation visits (delivered face to face or online) online by the central CTU trial team.

### 26.5 Trial documentation

The trial office will provide an electronic Investigator File to each participating site containing the documents needed to conduct the trial. The trial office must review and approve any local changes made to any trial documentation including patient information and consent forms prior to use. Additional documentation generated during the course of the trial, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the trial.

## 27 ETHICAL AND REGULATORY CONSIDERATIONS

### 27.1 Declaration of Helsinki

The Investigator will ensure that the trial is conducted in accordance with the principles of the Declaration of Helsinki.

### 27.2 Guidelines for Good Clinical Practice

The Investigator will ensure that the trial is conducted in accordance with relevant regulations and with the principles of Good Clinical Practice.

### 27.3 Ethical conduct of the trial and ethical approvals

The protocol, patient information sheet, informed consent form and any other information that will be presented to potential trial participants (e.g. advertisements or information that supports or supplements the informed consent process) will be reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC).

### 27.4 NHS Research Governance

Once HRA, HCRW & NRS approval is in place for the trial, sites will confirm capability and capacity to participate in the trial.

### 27.5 Protocol amendments

All amendments will be generated and managed according to the trial office standard operating procedures to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC and local approvals must be in place prior to implementation by Investigators as applicable for the amendment type. The only exceptions are for changes necessary to eliminate an immediate hazard to trial participants (see below).

It is the Investigator's responsibility to update participants (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the participant's willingness to continue in the trial. The Investigator must ensure this is documented in the participant's medical notes and the participant is re-consented if appropriate.

### 27.6 Protocol Compliance and Deviations

Protocol compliance is fundamental to GCP. Prospective, planned deviations or waivers to the protocol are not allowed. Changes to the approved protocol need prior approval unless for urgent safety reasons.

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Deviations from the protocol will be captured within the trial database either using a protocol deviation form or via suitably designed fields within the CRF which will be extracted from the trial database and reviewed regularly by the Trial Management Group (TMG). Deviations will be handled and reviewed in a timely manner in accordance with a trial-specific Data Management and Monitoring Plan.

The investigator must promptly report any important deviation from Good Clinical Practice or protocol to the trial office. Examples of important deviations are those that might impact on patient safety, primary/ secondary endpoint data integrity, or be a possible serious breach of GCP (see section 27.9).

### 27.7 Urgent safety measures

The sponsor or site Principal Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The trial may continue with the urgent safety measures in place. **The Investigator must inform the trial office IMMEDIATELY if the trial site initiates an urgent safety measure:**

The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The site Principal Investigator will provide any other information that may be required to enable the trial office to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out. The Trial office will follow written procedures to implement the changes accordingly.

### 27.8 Temporary halt

The sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **or** to declare a temporary halt. A temporary halt is defined as a formal decision to:

- interrupt the treatment of participants already in the trial for safety reasons;
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the trial in a timely manner.

The trial office will report the temporary halt via an expedited substantial amendment procedure. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

### 27.9 Serious Breaches

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree (a) the safety or physical or mental integrity of the trial subjects; or (b) the scientific value of the research.

Investigators must notify the Trial Office within one working day if any serious breach of GCP is suspected. The Trial Office will review the event and, if appropriate will report a serious breach to the REC, and the NHS host organisation within 7 days of the Trial Office becoming aware of the breach.

### 27.10 Trial reports

This protocol will comply with all current applicable Research Ethics Committee and Sponsor reporting requirements.

### 27.11 Transparency in Research

Prior to the recruitment of the first participant, the trial will be registered on a publicly accessible database (ISRCTN), which will be kept up to date during the trial, and results will be uploaded to the registry within 6 months of the end of the trial declaration. A Final Report will be submitted to the REC containing a lay summary of the trial results which will be published on the HRA website.

The results of the trial will be published and disseminated in accordance with the section 33.

### 27.12 Use of social media

Twitter feeds may be utilised to promote the trial, and acknowledge when milestones are met (e.g. sites open to recruitment, first recruitment ay a site etc).

## 28 PARTICIPANT CONFIDENTIALITY

### 28.1 Collection and use of personal identifiable information

Contact details (including date of birth, e-mail addresses/postal addresses/phone number) will be collected in this trial for the following purposes:

- Sending of follow-up questionnaires
- Sending of tablet computers directly to participant's homes (where requested)
- Sending a copy of the completed consent form by e-mail (for any participants and/or parent/guardian that consent electronically and wish to receive a copy by e-mail)

The patient information sheet explains what contact details will be collected and how these will be used; explicit consent will be obtained for this.

Parents/guardians of trial participants will be asked to provide their contact details.

Site staff at participating sites will ensure that contact details for trial participants are up to date when participants attend for trial visits.

Permission will also be requested from trial participants or their parent/guardian, as appropriate, to retain the participant's NHS/CHI number for long-term follow-up (up to five years), using routinely collected NHS data, from baseline (i.e. from the time of consent/randomisation), to measure avoidance of surgery as a marker of treatment success. This is subject to additional funding.

### 28.2 Use of audio/visual recording devices

Not applicable for this trial.

### 28.3 Storage and use of personal data

Personal data during the trial will be stored and used in accordance with the Oxford Clinical Trial Research Unit's (OCTRU) Standard Operating Procedure for confidentiality, protection and breach of personal data in relation to research subjects. This ensures that all personal data collected during the trial is recorded, handled and stored in such a way that is satisfies the requirements of the UK General Data Protection Regulation and requires data to be anonymised as soon as it is practical to do so.

All electronic patient-identifiable information will be held on a secure, password-protected database accessible only to authorised personnel. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area. The processing of the personal data of participants will be minimised wherever possible by the use of a unique participant trial number on trial documents and any electronic databases.

Personal data on all documents will be regarded as confidential. The trial staff will safeguard the privacy of participant's personal data.

The use of all personal data in the trial will be documented in a trial-specific data management and sharing plan which details what and where personal data will be held, who will have access to the data, when personal data will be anonymised and how and when it will be deleted.

The Investigator site will maintain the patient's anonymity in all communications and reports related to the research.

Data Breaches will be highlighted to the relevant site staff and reported as required by the UK GDPR and Data Protection Act 2018. This will also be deemed a protocol deviation.

### 28.4 Access to participants' personal identifiable data during the trial

Access to participants personal identifiable data will be restricted to individuals authorised to have access. This includes a) members of the research team at participating trial sites with delegated responsibility by the site Principal Investigator and b) members of the central CTU trial team involved in the conduct/management of the trial where this is necessary for their role.

Research staff that are not part of the participant's direct healthcare team will not have access to personal identifiable data until the participant has given their consent to take part in the trial or the participant has indicated to their direct healthcare team that they wish to be contacted by a member of the site research team – permission for this will be recorded in the participant's medical notes.

The patient information sheet clearly describes who will have access to the participants personal identifiable data during the trial and explicit consent is obtained from trial participants for such access.

Participants will be asked to consent to relevant sections of their medical notes and data collected during the trial being looked at by individuals from the University of Oxford, from regulatory authorities [and from the NHS Trust(s)/Board(s)], where it is relevant to their taking part in this trial; only authorised individuals will be granted access where this is necessary for their role.

### 28.5 Destruction of personal identifiable data

Explicit consent for the storage and use of personal identifiable data (which includes consent/assent forms) will be obtained from participants and/or their parent/guardian as detailed in the Participant Information Leaflet and Informed Consent Form.

Personal identifiable data will be destroyed as soon as it is no longer required – the time point for this destruction is detailed in the trial DMP and is in accordance with OCTRU standard operating procedures which comply with the UK GDPR.

### 28.6 Participant Identification Log

The site research team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

## 29 PUBLIC AND PATIENT INVOLVEMENT

### 29.1 PPI in design and protocol development

Patient and Public Involvement (PPI) has been central to the design of the ROBUST trial. Young people and their families have been involved in the development of this trial and the trial protocol in a number of ways. Our young person and parent co-applicants had input to the funding application for the trial (including format of the intervention and choice of primary outcome) and will contribute throughout its duration. We had a meeting and received input from Generation-R (network of young people supporting design of paediatric research in the UK) on acceptability of the intervention and how to engage young people with CP. The trial design was influenced by our: 1. Focus groups and interviews conducted to define a COS for lower limb surgical interventions in young people with CP (28); 2. Interviews with adolescents about their experience of participating in a progressive resistance training programme (46).

So far, taking into account the above, approximately 50 children and parents have had a notable influence on our design. Here is what we have learned through this process:

- The outcomes that are important for young people and their families.
- The way progression of ability through exercise motivates adolescents.
- How a "star chart" or equivalent reward system can motivate young people.
- The importance of motivating parents through providing relevant information.
- A suggestion of progression through different levels of difficulty, similar to those on video games.
- The acronym of the trial – ROBUST.
- The need to advise all trial participants of the results of the trial when it is completed. This has to be in a comprehensible and age appropriate manner.

### 29.2 PPI in managing, undertaking and disseminating the trial findings

The trial will be co-produced with adolescents and their families. To this effect we will involve their representatives with the TMG and TSC during the course of the trial. We will monitor recruitment and will be reviewing progress of the trial with our parent/children partners. This will ensure that the trial remains patient-focused throughout. In particular, we will consult with our parent/child co-investigators in relation to any changes to the protocol that might prove necessary during the course of the trial or any safety or adverse event issues. We have set up a Young People and Patient/Public

Advisory Group (YP/PAG) of 5 parents and 5 young people to support the trial. The PPI lead and YP/PAG will take a lead role in monitoring engagement of children and families from underserved areas. One of the clinical co-applicants (GF) will act as link for Equality, Diversity and Inclusion and will assist the PPI team in this task.

We will work with young people at the setting-up stage to produce information material for the trial, which is age appropriate and engaging. We have planned two meetings during the setting-up stage to this effect. We will set-up the trial website with the help of young people to include easily accessible material containing information for the trial and to provide a communication platform for actual participants to engage, communicate and feedback to the research team.

Our parent/child co-investigators and PPI panel, with assistance from the NIHR young-persons advisory group, will lead on the dissemination of the trial results to patients and the wider public. To inform patients and the public, we intend to produce a lay summary, which will be made available to the participating hospitals and to patients involved in the trial. In accordance with the Generation R advice, we will ensure that the children and young people involved in the trial are communicated the results in a format that is accessible to them. In addition, we will publicise the work through social media outlets (facebook and twitter), podcasts and blogs, as well as websites such as patient.info. We will consult with young people and parents on optimal ways to communicate the results of the trial to the wider public and the media.

## 30 EXPENSES/PAYMENTS TO PARTICIPANTS

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts or a mileage allowance provided as appropriate.

## 31 SPONSORSHIP, FINANCE AND INSURANCE

### 31.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship.

### 31.2 Funding and support in kind

The table below provides a summary of all funding and support in kind for the trial.

| **Funder(s)** | **Financial and non-financial support given** |
|---|---|
| National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme | NIHR135150 |

### 31.3 Insurance

The Sponsor (University of Oxford) has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

## 32 CONTRACTUAL ARRANGEMENTS

This trial is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate.

The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the trial as appropriate.

## 33 PUBLICATION AND DISSEMINATION

Publication and dissemination of trial results and associated trial publications (e.g. the trial protocol, statistical analysis plan (SAP) will be in accordance with OCTRU Standard Operating Procedures and irrespective of trial findings.

The findings from the trial will inform NHS clinical practice for the management of ambulant adolescents with spastic CP. The trial will be prospectively registered, prior to ethics approval, on the International Standard Randomised Controlled Trial Number register. The trial protocol will be available via the NIHR HTA website and published in an open-access peer-reviewed journal in accordance with the SPIRIT Statement (www.spirit-statement.org/). The trial results will be published as a final report/monograph as part of the NIHR HTA journal series. They will also be published in a high impact open-access journal, in accordance with the NIHR's policy on open-access research. The trial results will be reported following the CONSORT guideline (www.consort-statement.org), in particular the extensions for non-pharmacological interventions and patient-reported outcomes. Many published trials of exercise and physiotherapy interventions fail to provide a comprehensive description of the intervention under investigation, making it difficult for others to replicate the same interventions. We will use the TIDieR Statement (47) for reporting the intervention, ensuring that replication is possible. All trial materials, including the physiotherapist training materials and high quality patient advice materials, will be made freely available via the trial website.

### 33.1 Dissemination of trial results to participants

Prior to formal publication, we will inform the adolescents and their parent/guardian(s) of the trial results using explainer videos and infographics to support written information. The participants will be asked how they would like to be informed of the trial results as part of their original consent process. Our Patient and Public Involvement representatives will help inform how best to disseminate the trial results to other young people with CP and to the wider public. We will also host an Investigator Day to feed the trial results back to the physiotherapists and other members of the team at the trial sites. We will link with the CPIP network, the British Society for Children's Orthopaedic Surgery, British Academy of Childhood Disability and the Association of Paediatric Chartered Physiotherapists to ensure the results are communicated to all relevant professionals.

### 33.2 Authorship

Authorship of any publications arising from the trial will be determined in accordance with the ICMJE guidelines and any contributors acknowledged accordingly.

All publications arising from this trial must acknowledge the contribution of the participants, funder, OCTRU, SITU and the Sponsor.

## 34 DEVELOPMENT OF A NEW PRODUCT/PROCESS OR THE GENERATION OF INTELLECTIAL PROPERTY (IP)

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

## 35 ARCHIVING

### 35.1 Minimum Mandatory archiving period

It is the University of Oxford's policy to store data for a minimum of 3 years following publication. For the ROBUST trial we will intend to store data for up to 5 years, to allow for long term follow up.

Investigators may not archive or destroy trial essential documents or samples without written instruction from the trial office.

### 35.2 Retention of documents beyond the mandatory archiving period

The following documents will be retained longer; explicit consent for this retention will be obtained from participants:

- Informed consent /assent form for the purpose of long term follow up outside the duration of the trial

### 35.3 Archiving responsibilities/procedure

During the trial and after trial closure the Investigator must maintain adequate and accurate records to enable the conduct of the trial and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request for the minimum period as specified above.

#### 35.3.1 CTU Trial Master File

All paper and electronic data including the Trial Master File and trial database will be retained and archived in accordance with OCTRU's standard operating procedures which are compliant with the UK GDPR.

#### 35.3.2 Investigator Site File and participant medical records

The Investigator Site Files will be archived at the participating site. The medical files of trial participants must be retained for the mandatory archiving period stated above and in accordance with the maximum period of time permitted by the participating site. Sites should comply with the documentation retention specified in the clinical trial agreements (or equivalent) issued by the trial Sponsor.

### 35.4 Retention of data sets

Trial data and associated metadata electronically in a suitable format in a secure server area maintained and backed up to the required standard. Access will be restricted to the responsible Archivist and will be controlled by a formal access request. On completion of the mandatory archiving period the TMF and associated archived data sets will be destroyed or transferred as appropriate, according to any data sharing requirements.

## 36 DATA SHARING

The trial statistician may retain copies of anonymised datasets for the purpose of data sharing in accordance with the data sharing plan.

### 36.1 Retention of anonymised datasets

Upon completion of the trial, and with appropriate participant consent, anonymised research data may be shared with other organisations on request to the Chief Investigator and in accordance with the data sharing policies of OCTRU, the Sponsor and funder.

Summary results data will be available on the trial registration database within 6 months of the end of the trial. Requests for data (anonymised trial participant level data) will only be provided at the end of the trial to external researchers who provide a methodologically sound proposal to the trial team (and who will be required to sign a data sharing access agreement with the Sponsor) and in accordance with the NIHR guidance. After the end of the trial an anonymised trial dataset will be created and stored for as long as it is useful, and may be shared with other researchers upon request). Participant consent for this is included in the informed consent form for the trial.

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## 38 VERSION HISTORY

Previous versions of this protocol and a summary of the changes made are provided in the table below:

| Protocol version no. | Protocol date | Summary of key changes from previous version |
|---|---|---|
| 2.0 | 21Nov2023 | Section 16.2 and section 18 (table 4) have been edited to reflect that RRAMP will no longer be used for the trial. Randomisation will take place via the REDCap randomisation system accessed within the ROBUST REDCap trial database. The safety section in the protocol has been updated to include the process of safety reporting via REDCap and to clarify the reporting process - this now reflects the wording of the OCTRU CTU non-CTIMP version template protocol. Finally, the Re-Consent section (15.6) has now been edited to clarify the role of the site team in this process. |
| 3.0 | 12Dec2024 | Section 11 now includes details of a sub-study exploring monetary incentives for increasing participant retention rates. The sub-study protocol has been added to the appendix (3). In addition to this change, we have amended the text, where relevant, to reflect that other members of the research team (besides the physiotherapists) can complete the baseline clinical assessments. We have added the option to complete the informed consent process remotely (section 15) and we have included a 'Remote Consent Flowchart', for clarity. Finally, we have removed text on pages 13 and 15 as this was previously included in error. |
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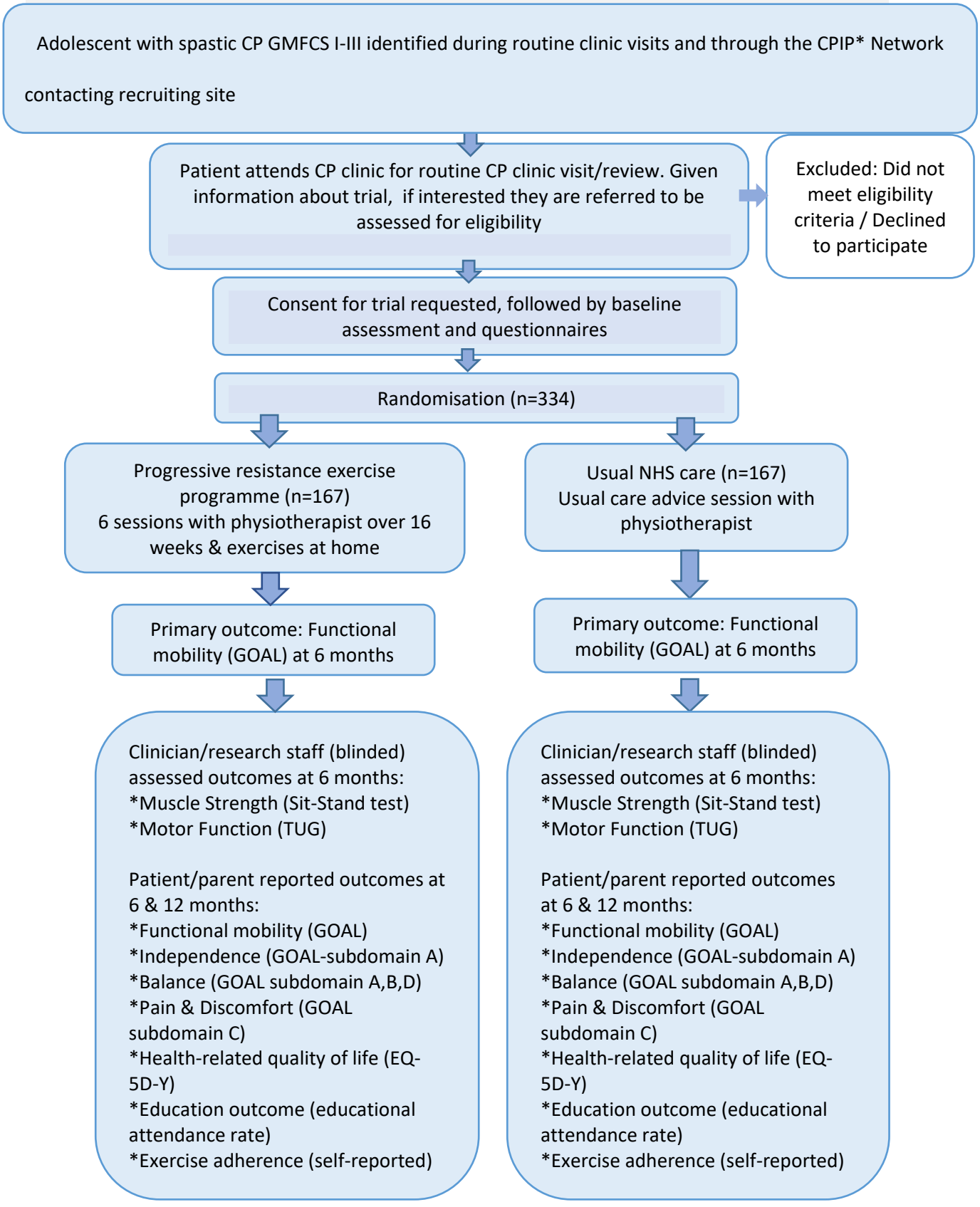
**APPENDIX 1 –TRIAL FLOW CHART**




**CPIP: Cerebral Palsy Integrated Pathway; GOAL: Gait Outcomes Assessment List*

## APPENDIX 2 – NIHR HTA COMMISSIONING BRIEF



NIHR | National Institute for Health Research

# 21/23 Strengthening programme for ambulant adolescents with cerebral palsy commissioning brief

## Introduction

The aim of the Health Technology Assessment (HTA) Programme is to ensure that high quality research information on the clinical effectiveness, cost-effectiveness and broader impact of healthcare treatments and tests are produced in the most efficient way for those who plan, provide or receive care from NHS and social care services. The commissioned workstream invites applications in response to calls for research on specific questions which have been identified and prioritised for their importance to the NHS, patients and social care.

## Research question

**What is the clinical effectiveness of a strengthening programme for ambulant adolescents with cerebral palsy?**

- **Intervention:** Adolescent-specific strengthening or progressive resistance therapy programme (applicants to define and justify).
- **Patient group:** Ambulant adolescents with spastic cerebral palsy (applicants to define and justify their eligibility criteria, including age).
  Applications are encouraged which include recruitment from geographic populations with high disease burden which have been historically underserved by research activity in this field.
- **Setting:** Clinical/community setting.
- **Comparator:** Usual practice fitness or physical activity programme without specific strengthening exercises (applicants to define and justify).
- **Study design:** A randomised controlled trial with an internal pilot phase to test key trial processes such as recruitment and adherence. Clear stop/go criteria should be provided

to inform progression from pilot to full trial.

- **Important outcomes:** Activities of daily living (including participation in recreation); gross motor function; gait; measurements of strength.
- **Other outcomes:** Patient and carer acceptability; treatment fidelity; adherence; independence; balance; educational outcomes; quality of life; adverse effects. Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise.
- **Minimum duration of follow-up:** Six months.
- **Longer-term follow up:** If appropriate, researchers should consider obtaining consent from participants to allow potential future follow up through efficient means (such as routine data) as part of a separately funded study.

## Rationale

Cerebral palsy (CP) is a lifelong condition affecting movement and co-ordination. It is caused by a problem with the brain that occurs before, during, or shortly after birth, such as a reduction in oxygen supply. It is estimated to affect one in every 400 children in the UK. The underlying brain damage which causes CP will not change over time, but the effects it has on the individual will. Gross motor skills (GMS) such as sitting and walking can improve in early to mid-childhood, levelling off in adolescence and may begin to decline in young adulthood. GMS directly impact on a child and young person's ability to participate in many aspects of daily living and therefore it is important to maintain GMS for as long as possible.

Physiotherapy is one of the most important treatments for children and adolescents with CP and involves exercises to maintain and hopefully improve movement. Strength or progressive resistance therapy for legs may include, for example, leg press and sit-to-stand exercises. Whilst strengthening exercises are currently widely used, there is a lack of standardisation of both the specific programmes and usual care. As adolescence is a time when young people with CP are likely to lose function, it is important that young people with CP are participating in exercise which is most beneficial to them in terms of maintaining the function they already have.

As such, the British Academy of Childhood Disability Strategic Research Group in conjunction with the Castang Foundation identified this as one of the top research priorities to address the number one uncertainty identified by the James Lind Alliance Childhood Disability Research Priority Setting Partnership. Applications should be co-produced, demonstrating an equal partnership with service commissioners, providers and service users (including carers) in order to provide evidence and actionable findings of immediate utility to decision-makers, should be embedded throughout the life cycle of the project from application to completion. Applicants may wish to consult the NIHR INVOLVE guidance on co-producing research.

A separate call is available for a stretching programme for ambulant children with cerebral palsy: applicants should consider whether synergies between the two calls offer opportunities for efficiency, and we would welcome applicants to propose shared infrastructure between the two calls.

## Additional commissioning brief background information

A background document is available that provides further information to support applicants for this call. It is intended to summarise what prompted the call and the existing evidence base, including relevant work from the HTA and wider NIHR research portfolio. It was researched and written on the basis of information from a search of relevant sources and databases, and in consultation with a number of experts in the field. If you would like a copy please email htaresearchers@nihr.ac.uk.

## Making an application

If you wish to submit a Stage 1 application for this call, the online application form can be found on the funding opportunities page. To select this call, use the filters on the right of the screen or search using the call name and/or number.

Your application must be submitted on-line no later than 1pm on the 28 July 2021. Applications will be considered by the HTA Funding Committee at its meeting in September 2021.

Guidance notes and supporting information for HTA Programme applications are available by clicking the links.

**Important**: Shortlisted Stage 1 applicants will be given eight weeks to submit a Stage 2 application. The Stage 2 application will be considered at the Funding Committee in January 2022.

**Applications received electronically after 1300 hours on the due date will not be considered.**

For commissioned topics, the Programme strongly discourages the practice of the same co-applicant joining more than one competing team. There may be unusual circumstances where the same person could be included on more than on application eg a lead from a named charity or a unique national expert in a condition.

For such exceptions (i) each application needs to state the case as to why the same person is included (ii) the shared co-applicant should not divulge application details between teams and (iii) both teams should acknowledge in their application that they are aware that one of their co-applicants is part of a competing application and that study details have not been shared.

**Should you have any queries please contact us at** htacommissioning@nihr.ac.uk.

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## APPENDIX 3 – ROBUST SUB-STUDY

# Implement SWATs in SPELL and ROBUST: The effectiveness and cost-effectiveness of monetary incentives for increasing participant retention rates in the SPELL and ROBUST trials - simultaneous Study Within A Trial protocol

| | ISRCTN | IRAS Reference | Ethics Reference | Funder reference |
|---|---|---|---|---|
| **ROBUST** | ISRCTN68282588 | 325313 | 23/SC/0231 | NIHR135150 |
| **SPELL** | ISRCTN15808719 | 326645 | 23/EE/0153 | NIHR135131 |

### Objective of this SWAT

1) To evaluate:

- a) the effectiveness of an unconditional £10 gift voucher incentive versus no monetary incentive (6-month follow up) for increasing participant retention rates in the SPELL and ROBUST trials
- b) the effectiveness of unconditional £10 gift vouchers incentives given at two times points (6- and 12-month follow-up) versus a £10 gift voucher incentive at one time point (12-month follow-up only) for increasing participant retention rates in the SPELL and ROBUST trials

2) To evaluate the cost effectiveness of these monetary incentive strategies.

### Study area

Retention, Follow-up

## Background

### Monetary incentives as a potential strategy for improving retention rates in trials

Poor participant retention rates can have adverse consequences on the internal validity of randomised trials. There is a lack of evidence on efficient ways to retain participants in trials. One solution is to use a randomised 'Study Within A Trial' (SWAT) design, where a randomised trial is embedded within another trial. This method, done within a single host trial or across several in a coordinated way, can produce rapid, high-quality evidence.

Monetary incentives consisting of either shopping/gift vouchers or cash are a common strategy used by trial teams to encourage participants to complete follow-up questionnaires, attend follow-up assessment appointments or both. The Cochrane methodology review of strategies to improve retention in trials found monetary incentives may improve retention rates compared with no incentive; but the certainty of the evidence was low [1]. Another Cochrane methodology review focused on increasing response to postal and electronic questionnaires in all types of research studies, found that offering unconditional incentives (i.e., giving participants the incentive without requiring them to complete the questionnaire first) is more effective than conditional incentives, which are contingent on participants completing and returning questionnaires [2]. The Cochrane review of retention strategies in trials, the James Lind Alliance retention priority setting exercise [3], and work undertaken by Implement SWATs and the Trial Forge SWAT Network have all highlighted monetary incentives as a priority for evaluation. Patient and public involvement (PPI) work suggests that whilst patients view monetary incentives as both ethical and a priority strategy for testing using SWATs, some adult patient populations may be more likely to prefer cash than a shopping voucher, and may respond differently to cash and voucher incentives. On the other hand, PPI undertaken with the SPELL and ROBUST partners identified that for children and young people, offering vouchers as incentives rather than cash may be more appropriate.

Assessments of the effectiveness and cost effectiveness of monetary incentives versus no incentive on retention rates would help trial teams to make evidence-informed decisions about whether to use monetary incentives; and if so, whether to offer this on a one-off basis at one follow-up timepoint, or at multiple timepoints.

## Implement SWATs

Implement SWATs (Using IMPLEMENTation science and Studies Within A Trial to improve evidence-based participant recruitment and retention in randomised controlled trials) is a national programme funded by the National Institute for Health and Care Research (NIHR). Implement SWATs aims to develop and promote the use of evidence for recruiting and retaining participants in trials, using SWAT methodology and is undertaking a coordinated programme of monetary incentive SWATs across approximately 20 different host trials and patient populations to provide high-quality evidence at speed. More about Implement SWATs can be found at: www.implementswats.org.

As part of its coordinated SWATs programme, Implement SWATs is collaborating with the SPELL and ROBUST trials (funded by NIHR) teams to provide funding and support to test the effectiveness and cost-effectiveness of monetary incentives for retaining trial participants.

## The host trials: SPELL and ROBUST

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### Full host trial title: SPELL

Clinical effectiveness of a child-specific dynamic stretching programme, compared to usual care, for ambulant children with spastic cerebral palsy (SPELL trial): a parallel group randomised controlled trial.

Short title: Stretching programme for ambulant children with cerebral palsy (SPELL)

### Trial aim: SPELL

To assess the clinical effectiveness of a child-specific dynamic stretching programme, compared to usual care, for ambulant children with spastic cerebral palsy.

### Study design: SPELL

The SPELL trial is a multi-centre, two arm, parallel design, superiority, randomised controlled trial. The participants will be individually randomised (1:1) to receive either a dynamic stretching intervention programme or usual NHS care.

### Participants and setting: SPELL

The SPELL trial will recruit 334 children (167 in each arm) from 4 to 11 years of age (i.e. from their 4th birthday to the day before their 12th birthday) with a diagnosis of spastic cerebral palsy (bilateral or unilateral) Gross Motor Function Classification System (GMFCS) levels I–III who are able to comply with assessment procedures and exercise programme with or without support by their carer.

Participants will be identified through the Cerebral Palsy Integrated Pathway (CPIP) Network and recruited from approximately 12 NHS Trusts/Health Boards in hospital and community settings providing care for children and young people with cerebral palsy.

### Intervention: SPELL

Dynamic stretching exercise programme: Participants receive an individually tailored dynamic stretching programme overseen by a physiotherapist via 6 one-to-one sessions over 16 weeks.

### Control: SPELL

Usual NHS care: Participants receive an assessment with a physiotherapist and are provided with NHS advice on self-management, including access to supporting information and continuation of any usual exercise, fitness/physical activity programme (as applicable).

### Outcomes and follow-up: SPELL

To assess whether an individually tailored dynamic stretching programme overseen by a physiotherapist over 16 weeks, improves functional mobility in ambulant children with spastic CP compared with usual care, functional mobility at 6 months will be measured using the patient/parent reported GOAL (Gait Outcomes Assessment List) questionnaire.

Each participant will be followed up for 12 months from randomisation, with assessments at baseline, 6- and 12- months post-randomisation.

### Planned host trial period: SPELL

The planned trial period is 44 months, with recruitment starting on 20th November 2023 and expected to last for 20 months. Planned reporting date is 31st August 2026.

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## Full host trial title: ROBUST

Clinical effectiveness of an adolescent-specific strengthening programme, compared to usual care, for ambulant adolescents with spastic cerebral palsy (ROBUST trial): a parallel group randomised controlled trial.

Short Title: Strengthening programme for ambulant adolescents with cerebral palsy (ROBUST).

### Trial aim: ROBUST

To assess the clinical effectiveness of an adolescent-specific strengthening programme, compared to usual care, for ambulant adolescents with spastic cerebral palsy.

### Study design: ROBUST

The ROBUST trial is a multi-centre, two arm, parallel design, superiority, randomised controlled trial. The participants will be individually randomised (1:1) to receive either a strengthening intervention programme or usual NHS care.

### Participants and setting: ROBUST

The ROBUST trial will recruit 334 adolescents (167 in each arm) from 12 to 18 years of age (i.e. from their 12th to their 18th birthday) with a diagnosis of spastic cerebral palsy (bilateral or unilateral) Gross Motor Function Classification System (GMFCS) levels I–III who are able to comply with assessment procedures and exercise programme with or without support from their carer.

Participants will be identified through the Cerebral Palsy Integrated Pathway (CPIP) Network and recruited from approximately 12 NHS Trusts/Health Boards in hospital and community settings providing care for children and young people with cerebral palsy.

### Intervention: ROBUST

Progressive resistance exercise programme: Participants receive an individually tailored strengthening programme, including structured resistance exercises and advice, overseen by a physiotherapist with 6 one-to-one sessions over 16 weeks.

### Control: ROBUST

Usual NHS care: Participants receive an assessment with a physiotherapist and are provided with NHS advice on self-management, including access to supporting information and continuation of any usual exercise, fitness/physical activity programme (as applicable).

### Outcomes and follow-up: ROBUST

To assess whether an individually tailored strengthening programme overseen by a physiotherapist over 16 weeks, improves functional mobility in ambulant adolescents with spastic cerebral palsy compared with usual care, functional mobility at 6 months will be measured using the patient/parent reported GOAL (Gait Outcomes Assessment List) questionnaire.

Each participant will be followed up for 12 months from randomisation, with assessments at baseline, 6 and 12 months post-randomisation.

### Planned host trial period: ROBUST

The planned trial period is 44 months, with recruitment starting on 3rd January 2024 and expected to last for 20 months. Planned reporting date is 31st August 2026.

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## Participants: monetary incentive SWAT

Participants will be eligible for this SWAT if they are enrolled in the SPELL or ROBUST trials and are prior to receiving their 6 month follow up questionnaire. This SWAT will focus on returns of the participant-completed questionnaires at 6 and 12 months post-randomisation.

### SWAT Intervention and comparators

1. **Intervention 1**: £10 shopping voucher incentive, given unconditionally before the 6-month and before the 12-month follow up questionnaire, sent by post. Participants in the intervention group will receive £20 in total.
2. **Intervention 2**: £10 shopping voucher incentive, given unconditionally before the 12-month follow up questionnaire only, sent by post.

The shopping voucher, and a cover letter encouraging completion of the follow up questionnaire, will be sent by the SPELL or ROBUST study team 2 weeks prior to the participant receiving their 6 month follow up questionnaire and, similarly 2 weeks prior to the participant receiving their 12 month follow up questionnaire.

### Method for allocating to intervention or comparator for SWAT

Eligible participants will be randomised using a centralised computer-generated 1:1 allocation ratio to one of the two interventions. The randomisation will be stratified by type of treatment allocation received within the host trial (active treatment or usual care) as it is theorised that it is possible that there may be a difference in retention between the host trial intervention arms. Variable block sizes will be used to ensure balance over the two SWAT interventions. Randomisation will be prepared by a statistician at the University of Oxford not involved in the preparation and distribution of the monetary incentive strategies and will be carried out separately for each host trial (SPELL and ROBUST).

### Outcome measures for SWAT

- Primary outcome: Retention rate, defined as the proportion of participants enrolled into the trial for whom outcome data are obtained at 6 and at 12 months.
- Secondary outcomes:
    - 1) Cost-effectiveness (cost per participant retained)
    - 2) Time to collection of outcome data (days from scheduled date)
    - 3) Number of reminders sent to participants before completion of follow-up assessment
    - 4) Questionnaire completeness (e.g., primary outcome measure obtained for the host trial)

Where possible, the effects of the strategies in different patient populations will be explored, including sex, age and ethnic subgroups.

### Sample size and power calculation for SWAT

The sample size will be determined by the number of participants due for follow-up at 6 and 12 months in the host trials from the point at which this SWAT is embedded and will be restricted by the total number to be recruited in each host trial (334 participants).

As single SWAT evaluations are not usually powered to show a small difference in effectiveness, due to their limited size, replications of a SWAT are needed in different settings and patient populations to enable a robust evaluation of effectiveness [4]. This SWAT is part of the NIHR funded Implement SWATs programme, which is undertaking a coordinated programme of monetary incentive SWATs across approximately 20 different host trials, so findings from this SWAT will be meta-analysed with those of other SWATs to provide a more robust estimate of their effectiveness.

### Blinding

It is not possible to blind research staff to the participant's allocation. Trial participants will be blinded to the SWAT hypothesis. To maintain blinding participants will not be informed about the SWATand will not be informed that they will receive payment, in the form of a shopping voucher, when asked to complete follow up questionnaires..

## Analysis plans for SWAT

Data will be analysed, by the SPELL and ROBUST study team and will be analysed separately for each host trial (SPELL and ROBUST). Demographic characteristics, including age, sex, and ethnic group, will be presented descriptively as mean (standard deviation) or number (%), as appropriate. An 'intention-to-treat' analysis will be performed including all randomised participants analysed in the SWAT group to which they were allocated. Any randomised participant who does not provide outcome data for any reason (including participants who were deceased or withdrawn from the host trial) will be categorised as 'Data not obtained' for the primary outcome.

To enable meta-analysis of our findings with those of similar studies of monetary incentives, anonymised, patient-level data from this SWAT will be shared with Implement SWATs team (funded by NIHR, award reference: NIHR302256), led by Dr Adwoa Parker, and based at York Trials Unit, University of York - a UKCRC registered Clinical Trials Unit (UKCRC Registration ID Number 40). The University of York has strict guidelines for data storage, access to study data and adherence to the principles of data protection (including the General Data Protection Regulation). All datasets will be anonymised before transfer to the University of York, removing all identifiable patient information such as names and addresses, and will be encrypted before transmission to ensure security.

### Primary outcome analysis

Comparison of the questionnaire response rate between the two SWAT groups will use logistic regression. The regression model will be adjusted for the randomised group factor and the SWAT stratification factor (i.e., host trial intervention arms). The between-groups difference will be presented as a number (%) and as both adjusted absolute (i.e., risk difference) and relative (i.e., odds ratio or relative risk) effect estimates, with 95% confidence intervals from the logistic regression model.

### Secondary outcome analysis

The between-group difference in time taken to collection of outcome data will be analysed using techniques suitable for time to response (event) data such as Kaplan-Meier curves, log-rank test or Cox regression (adjusted for SWAT stratification/minimisation factors). Time zero will be set as 'day before expected completion date' (equivalent to adding 1 to the time variable to avoid exclusion from the analysis set).

The analysis of questionnaire completeness will be as for the primary outcome.

The incremental cost per participant retained will be calculated for the comparisons under evaluation as the difference in costs between the SWAT groups, divided by the difference between groups in completion rates. Direct costs of the retention strategies, and indirect costs associated with administering the strategies and the comparators will be included.

The following sensitivity analyses will be performed for the primary analysis:

- Excluding participants who did/could not receive allocation as randomised.
- Excluding participants who were retrospectively found to have died or withdrawn from the host trial before the expected completion date.

Subgroup analysis may also be performed for key demographic subgroups (e.g. age, sex, ethnicity) by adding interaction terms to the logistic regression or Cox regression model, where the sample size is deemed sufficiently large.

Meta-analyses will include data from existing SWATs and will estimate differences in retention rates between the intervention and comparator groups. Within the meta-analysis, remote self-completion of questionnaires by trial participants and face-to-face data collection should be evaluated in subgroups and a

combined treatment effect should be presented only if it is deemed that the effects are homogeneous between subgroups.

## Patient and public involvement (PPI)

This SWAT was developed in collaboration with patients and public partners, including the Implement SWATs PPI Group, which consists of nine adult men and women of differing ages, ethnicity and health conditions. PPI members identified monetary incentives as a priority strategy to test for recruiting and retaining participants, and have informed the design and content of this SWAT. The group has provided detailed input into the relevance of the research question, the SWAT interventions, outcomes, ethics, logistics of the SWAT as well as dissemination of findings. All members of the PPI group view this SWAT as both ethical and a priority question to test. However, the PPI work also identified that some adult patient populations may be more likely to prefer one format of incentive (e.g., cash than a shopping voucher), and may respond differently to cash and voucher incentives.

For children and young people, PPI partners from SPELL and ROBUST suggested that vouchers would be better for this age group than cash. They also suggested that £5 was too small an incentive, with £10 or £20 being a good amount of incentive to offer. They were keen that all participants in SPELL and ROBUST should receive some form of financial incentive. Given the limitation on funding, the PPI partners agreed to test the effectiveness of a £10 voucher for the main intervention.

## Possible problems in implementing this SWAT

The need for ethical approval before using the incentives and logistical difficulties in administering the shopping voucher incentive.

## Contact details for the Implement SWATs team

- Email: swats-group@york.ac.uk
- The Implement SWATs Chief Investigator, Dr Adwoa Parker can also be contacted by email at adwoa.parker@york.ac.uk, Tel: 01904 32 1671
- Website: www.implementswats.org

## Funding and Sponsor statement

The SPELL and ROBUST Trials are funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment Programme (SPELL - NIHR135131; ROBUST-NIHR135150) and Sponsored by the University of Oxford. University of Oxford will act as Sponsor for this SWAT as this will be embedded within the SPELL and ROBUST host trials.

Implement SWATs is Sponsored by the University of York (UK) and funded by the NIHR (Dr Adwoa Parker's Advanced Fellowship, reference: NIHR302256). Only anonymised, patient-level data from this SWAT will be shared with the Implement SWATs team at the University of York, as such the University of Oxford will act as data controller and University of York as the data processor.

The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

## References

1. Gillies K, et al. Strategies to improve retention in randomised trials. Cochrane Database of Systematic Reviews 2021;(3):MR000032.
2. Edwards PJ, Roberts I, Clarke MJ, DiGuiseppi C, Woolf B, Perkins C. Methods to increase response to postal and electronic questionnaires. Cochrane Database of Systematic Reviews 2023, Issue 11. Art. No.: MR000008. DOI: 10.1002/14651858.MR000008.pub5. Accessed 12 January 2024.

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4. Treweek S, Bevan S, Bower P, Briel M, Campbell M, Christie J, Collett C, Cotton S, Devane D, El Feky A, Galvin S, et al. Trial Forge Guidance 2: how to decide if a further Study Within A Trial (SWAT) is needed. Trials. 2020 Dec;21(1):1-9.