BMJ Open How does the intensity of physical therapy affect the Gross Motor Function Measure (GMFM-66) total score in children with cerebral palsy? A systematic review protocol

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ABSTRACT

Introduction Intensive physical therapy (PT) interventions administered to children with cerebral palsy (CP) have received a significant amount of attention in published literature. However, there is considerable variability in therapy intensity among studies and notable lack of information on optimal intervention dosing. This makes it difficult for clinicians to use evidence to inform practice. Many studies use the Gross Motor Function Measure (GMFM-66) to assess functional progress in children with CP. The purpose of this systematic review will be to identify the GMFM-66 change score reported in published studies, with outcomes based on intervention intensity. Whether the type of PT intervention, child's age, and Gross Motor Function Classification System level influence the GMFM-66 scores will be also assessed.

Methods and analysis This systematic review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 checklist. In March 2018, nine databases (PubMed, Ovid MEDLINE, Cochrane Library, Embase, Scopus, Web of Science, CINAHL, ClinicalTrials.gov, and REHABDATA) were searched for controlled clinical trials and single-subject design studies of PT interventions of any kind and intensity that used the GMFM-66 as an outcome measure for children with CP, age up to 18 years. Two authors independently reviewed the titles and abstracts and arrived at consensus on paper selection for a full-text review. The same process was used for a full-text article screening based on further detailed inclusion criteria, with a final selection made for those suitable for data extraction. Prior to commencement of data extraction, all searches will be updated, and new results re-screened.

Ethics and dissemination This study will involve a systematic review of published articles and no primary data collection. Therefore, no ethical approval will be necessary. Results will be disseminated in a peer-reviewed publication and presented at scientific conferences.

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INTRODUCTION

Physical therapy (PT) for children with cerebral palsy (CP) includes a wide variety of interventions. Evidence supporting these

Strengths and limitations of this study

- The broad definition of physical therapy intervention used in this systematic review will allow for an appraisal of a large body of research.
- This systematic review will use rigorous PRISMA-P guidelines to investigate which interventions administered at what dose, and at what age may result in the most functional gain in children with cerebral palsy of different levels of severity.
- Title and abstract screening, as well as the full-text article screening in this systematic review were performed by two independent reviewers, with disagreements resolved by consensus.
- During this systematic review, data extraction, risk of bias assessment and evaluation of the quality of evidence will be performed by two independent reviewers and verified by a third reviewer.
- It is expected that the heterogeneity of reviewed research reports will preclude the performance of meta-analyses of data and may make the study groupings and related comparisons difficult.

interventions varies in its level and quality, as do the PT frequency and duration parameters. Intensive interventions administered to children with CP have received a significant amount of attention in the published literature. However, there is considerable variability both in the type of therapeutic intervention and the intensity with which it is administered and at what age,¹ and a notable lack of information on the optimal intervention dosing.^{2,3} This makes it difficult for clinicians to use evidence to inform practice and to define the 'standard of care' for this patient population. The rationale for early intensive therapy and examples of related studies are provided below.

Rationale for PT started early and administered with intensity

The rationale for an intensive series of active, repetitive, task-specific therapies is based on what is known about brain plasticity as seen in animal studies,⁴ rehabilitation interventions in adult stroke survivors⁵ and investigations in children with unilateral CP, often secondary to a 'perinatal stroke'.^{6,7} Cortical reorganisation is influenced by several factors: the precise location and size of the lesion, the age at which the injury occurred, and the nature and extent of the rehabilitative training.⁴

Reorganisation can occur in one of three ways: by recruitment of undamaged neurons adjacent to the injured neurons, by recruitment of neurons from supplemental non-primary motor areas, or by stimulation of ipsilateral neurons.⁴ If the lesion involves a small area, the immediate adjacent territory is reprogrammed for the lost function. If the lesion is larger and involves the adjacent territory, reprogramming may recruit premotor cortical areas. Surgical lesions in newborn monkeys initially result in motor dysfunction, but function gradually returns as the areas adjacent to the damaged ones are reprogrammed to assume the function of damaged neurons. If the lesion is very large, the intact opposite hemisphere may be recruited.⁴ The latter situation is most dramatic in the young child who has undergone a hemispherectomy as radical treatment for uncontrolled seizures.⁸ Within days, the child is walking and shows only mild signs of hemiparesis. This is probably the result of intact ipsilateral connections but also of the removal of abnormal discharges from the contralateral dysfunctional hemisphere.⁸

The pathophysiology of an adult stroke is very similar to a perinatal stroke that has resulted in hemiparetic CP. Even in the older brain, repetitive motor skill-directed rehabilitation promotes brain plasticity, can restore some function, and is represented by an enlarged area of the motor cortex.⁹ With no rehabilitation, there is scant improvement in function and no increase in the cortical map representation. Restriction of movement in the strong arm and hand of a stroke survivor for as little as 10 days improves function of the paretic arm, and a corresponding enlargement of the cortical representation of that upper extremity is observed. In contrast, non-use of the paretic limb results in a decrease in the corresponding cortical representation.⁹ Similar findings have been reported in children with unilateral CP, with constraint-induced therapy administered for just 6 hours a day for 10 days.¹⁰

The fact that a young brain is more adaptable, with greater neural plasticity potential than an older brain, is due to several factors.^{10,11} Because there is less myelin in the young brain, the neurons have a better potential to repair themselves.¹¹ This, combined with the abundance of trophic factors that stimulate nerve growth, supports neural plasticity in the younger compared to an older brain.^{10,11}

Cortical reorganisation based on the principles of motor learning leads to sprouting of dendrites, formation of new synapses, alternation in existing synapses, and production of neurochemicals.¹² The type of rehabilitative therapies that will induce neural reorganisation was reviewed by Arya

*et al.*¹³ Changes are maximised and have long-term retention if rehabilitation is repetitive, intensive, and meaningful or skill oriented. For example, the cortical map representation of the index finger of a Braille reader is larger than that represented by the adjacent fingers and is larger than on the ipsilateral cortex. A person with bilateral upper extremity amputation who has learnt to use his right great toe to paint or sculpt shows an enlargement of the cortical area represented by the right great toe.¹⁴

Some basic principles are pertinent¹⁵ to the argument for early, intensive intervention: (1) There are critical times during neural development when a certain task is most easily learnt; (2) Reorganisation and reprogramming of neural tissue is use dependent ('use it or lose it'), and repetitive active movement has the greatest potential for stimulating neural growth; and (3) A young brain is more adaptable than an older brain.¹⁵

Examples of evidence for intensive intervention administered early

In 2010, Arpino *et al.*¹⁶ reported on a meta-analysis of intensive PT in children with CP and found only three studies that satisfied their criteria for a randomised clinical trial (RCT), which included having the word 'intensive' in the title, involving therapy frequency greater than three times a week, and using the Gross Motor Function Measure (GMFM)¹⁷ as the outcome measure.¹⁶ Bower *et al.*^{18,19} evaluated 56 children between 3 and 12 years of age, Gross Motor Function Classification System (GMFCS) level III or greater, all treated by a different therapist. These children showed a trend for improvement, but it did not reach statistical significance.^{18,19} The RCT by Tsorlakis *et al.*²⁰ involved 34 children between 3 and 14 years of age with mild to moderate CP (GMFCS levels I–III). There was a statistically significant difference found for the group that received the most intensive therapy (50 min sessions, 5 times a week, for 16 weeks).²⁰ Shamir *et al.*²¹ used a cross-over design to evaluate 10 patients, 12–22 months of age, and reported a gain of 7.8% on the GMFM for those receiving an intensive intermittent approach compared with a gain of 1.2% in those who received the standard of care therapy. The intensive intermittent therapy was administered four times per week for 90 min in week 1, followed by a 3-week rest period. The standard of care therapy included one 90 min session per week.²¹

Rationale for targeting the GMFM-66 change score in this review

Many of the published studies of PT interventions use the GMFM¹⁷ to assess progress in gross motor functional skills in children with CP. The GMFM-66 is a version of this instrument that is scored using a Gross Motor Ability Estimator (GMAE), a computer program that yields an interval-level total GMFM-66 score based on the individual test item scores entered by the examiner.¹⁷ Intervention intensity can be defined as a combination of intervention frequency and duration of therapy sessions provided over a specific period of time.^{22,23} Conducting a review of literature to identify the

GMFM-66 change score reported in published studies of PT intervention provided to children with CP, with outcomes based on PT intensity, may serve as a useful step toward determining which interventions administered at what dose and at what age may result in the most gross motor gain in children functioning at different GMFCS levels. It is important to note that a GMFM-66 score is a measure of motor capacity (what the child is capable of doing) and not a measure of motor performance that is defined by a combination of the child's observed physical activity and sedentary behaviour.^{24 25} Furthermore, changes in motor capacity after an intensive intervention may not be necessarily accompanied by changes in motor performance.^{24 26} Thus, the GMFM-66 change score targeted by this review will not reflect the effects of PT intervention on activity performance.

Objectives

The purpose of this systematic review will be to identify the GMFM-66 change score reported in published studies of PT interventions provided to children with CP, with outcomes based on intervention intensity. For the purposes of this review, intensive protocols will be defined as those administered at least three times per week, and their outcomes, described as the GMFM-66 change score, will be compared to those administered less frequently. Data on the duration of therapy sessions and the length of time over which the intervention was provided will be extracted and added to these comparisons if specific related groupings can be identified. The review will also assess how the type of PT intervention, as well as the child's age and GMFCS level may influence the functional outcome of intervention measured by the GMFM-66. This systematic review will be conducted to answer the following specific questions:

1. Do PT interventions provided to children with CP with a frequency of three times per week or greater result in a greater improvement in gross motor function, as measured by the change in GMFM-66 total score, than PT interventions provided less frequently?
2. Are greater GMFM-66 change scores reported in studies of PT interventions conducted in children with CP younger than 5 years of age compared to the GMFM-66 change scores of those who are 5 years of age and older?
3. Are children with mild to moderate CP (GMFCS levels I–III) more responsive to PT as indicated by the reported change in GMFM-66 total score than children with more severe CP (GMFCS levels IV and V)?
4. Which PT interventions produce the highest GMFM-66 change scores, as indicated by the results of published studies?

METHODS AND ANALYSIS

Design

This systematic review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 checklist.²⁷

Search strategy

An information specialist (CLH) searched the following databases from the year 2002, when the GMFM-66 was introduced, to the date the searches were run (14–15 March 2018): Ovid/MEDLINE, Elsevier/Embase, Elsevier/Scopus, Wiley/Cochrane Library, Clarivate/Web of Science (WOS), EBSCO/Cumulative Index of Nursing and Allied Health Literature (CINAHL), ClinicalTrials.gov and National Rehabilitation Information Center/REHABDATA. An English-language filter was applied.

The Ovid MEDLINE search strategy, on which the other database search strategies were based, is presented in online supplementary appendix. All records identified through the database searches were exported to the reference managing software EndNote versions X8–X9 (Clarivate Analytics, Philadelphia, PA, USA) which was used to document and delete the duplicate records.

Two independent reviewers (MR and BD) screened all titles and abstracts for relevance, with disagreements resolved by consensus. Full texts of all references that met the screening eligibility were similarly independently screened for inclusion by MR and BD according to the following inclusion/exclusion criteria, with disagreements resolved by consensus.

Inclusion criteria

1. GMFM-66 used as an outcome measure.
2. GMFM-66 total score reported.
3. Children of any age up to 18 years who had CP of any type and functional level.
4. Completed controlled clinical trials of PT intervention of any kind and any intensity, with the control group receiving any of the following:
 - No intervention.
 - A different type of PT intervention.
 - The same PT intervention of different frequency or supplemented with a medical intervention.
 - An alternative or complementary intervention.
5. Completed single-subject research design studies (SSRDs) of PT intervention, of any kind and intensity, with effects replicated across at least three subjects.
6. Only English-language publications.
7. Year of publication during or after 2002.

Exclusion criteria

1. Children who developed typically or had conditions other than CP.
2. Children identified as being at risk for CP.
3. Individuals with CP who were older than 18 years of age.
4. Non-experimental research
 - Correlation studies
 - Reliability studies
 - Review papers
 - Survey studies
5. Non-English-language publications.
6. Published protocols, results not yet reported.

Table 1 Data extraction variables

Participants	Intervention	Comparators	Outcomes
Age	Specific PT intervention used in the study	In group comparison studies (controlled clinical trials, randomised and non-randomised)	GMFM-66 total score
► <5 years	Frequency of intervention	► No intervention	► Initial
► ≥5 years	► <3 times per week	► A different type of PT intervention	► Final
Severity of cerebral palsy	► ≥3 times per week	► The same PT intervention of different frequency or supplemented with a medical intervention	► Change
► Mild to moderate (GMFCS levels I–III)	Duration of PT sessions (min)	► An alternative or complementary intervention	
► Severe (GMFCS levels IV–V)	Length of time intervention was administered (weeks)	In SSRDs, participants serve as their own controls	
	Adherence to protocol (% of the time)		

GMFCS, Gross Motor Function Classification System; GMFM-66, Gross Motor Function Measure; PT, physical therapy; SSRD, single-subject research design.

Prior to commencement of data extraction, all searches will be updated and new results re-screened. While we did not initially plan for a two-step search and selection process, it soon became evident that the overall time required to reach the data extraction stage would be considerably longer than initially projected. In order to maintain currency and have our review be as up to date as possible, we realised we would need to rerun the searches and have included that step in this protocol. Citations from relevant review articles and citations to and from all initially included articles will be searched and screened as well.

Data extraction

The variables that will be sought for group comparison studies and SSRDs are listed in [table 1](#) for each of the PICO items (Participants, Intervention, Comparators, and Outcomes). Data extraction will be completed by two investigators (BD, HLP), independently of each other, and verified by the third investigator (MR) who will lead a discussion of any identified discrepancies to reach consensus.

Outcomes and prioritisation

Primary outcome

The primary outcome will be the change in total GMFM-66 scores in children of any age up to 18 years, with a diagnosis of CP of any severity, who have had any type of PT with a frequency equal to or greater than three times per week, compared to a frequency of fewer than three times per week. This was prioritised based on the current understanding of brain plasticity, as dormant neurons are best stimulated and activated or recruited by the frequency of active movement.^{10 28}

Additional outcomes

We will also determine if the change in the GMFM-66 total scores based on intervention frequency is influenced by the following variables:

- Duration of PT sessions and the length of time (weeks) over which the intervention was administered.

These PT intervention parameters contribute to its intensity.^{22 23} However, defining intensive protocols based on all three related variables (frequency, duration and length of time over which the intervention was administered) may be difficult because of the anticipated high variability in intervention parameters among the studies. Nevertheless, if specific related groupings of published studies can be identified, the results of this review related to intervention intensity may be strengthened.

- The age of the child defined as ‘younger than 5 years’ or ‘5 years and older’.

This variable was prioritised based on the current understanding of brain plasticity, as dormant neurons are better stimulated and activated in ‘younger’ versus ‘older’ brains.^{10 15}

- The severity of CP defined by the GMFCS levels I, II or III (mild to moderate) or levels IV and V (severe).

An assumption has been made that children with CP of greater severity may have a larger-sized brain injury or a different precise area of injury.⁴ As discussed in the Introduction section of this paper, based on the current understanding of brain plasticity, the size and area of the injury determines the type of potential reprogramming.⁴

- Specific PT intervention used in the study.

As stated previously, there is a wide variety of PT interventions that are used in children with CP. Identifying which of these interventions have been documented to produce higher GMFM-66 change scores may provide valuable evidence that can be used to inform clinical practice.

Risk of bias in individual studies

Group comparison studies

To assess the risk of bias in group comparison studies, we will use the Physiotherapy Evidence Database (PEDro) scale to rate the methodological quality of RCTs that evaluate PT interventions.^{29–32} Maher *et al*³¹ demonstrated a fair to good reliability of the PEDro total score. In addition, de Morton³² found the PEDro scale to be a valid instrument for assessing methodological quality of clinical trials, and demonstrated that the PEDro total score can be considered interval-level data, which warrants the use of parametric methods of statistical analysis.

The PEDro scale consists of 11 items rated on a dichotomous scale (yes/no), with each 'yes' answer, except for item 1, assigned a score of 1, and each 'no' answer assigned a score of 0.^{29–30} The total score is calculated by adding the individual item scores for items 2–11. Item 1 pertains to the external validity of the clinical trial and is not used to calculate the PEDro score.^{29–30}

SSRD studies

To assess the methodological quality of SSRDs, we will use the rating scale developed by Romeiser Logan *et al*³³ specifically for single-subject design research. The scale authors reported a 75% agreement in obtaining the total score, which was comparable with the scales that are used to assess the methodological quality of group-design studies. The SSRD rating scale consists of 14 items scored on a dichotomous scale (yes/no), with a 'no' answer receiving a score of 0 and a 'yes' answer assigned one point except for items 5 and 8. Each of these two items represents a two-part question, and a 'yes' answer obtained for each part is assigned a score of 0.5. The total score is obtained by adding the individual item scores.³³

Other bias

All studies will be assessed for whether participants' evaluations using the GMFM-66 were performed following the specifications outlined in the test manual, including the use of the GMAE.²¹ In addition, the number of GMFM-66 items used to obtain the total score and whether this information was reported in the reviewed studies will be taken into account as an important quality criterion. Avery *et al*³⁴ found that a valid estimate of the child's gross motor function could be made by testing only 13 GMFM-66 items, which led to the development of the short forms of this test.³⁵ Nevertheless, the GMFM-66 authors recommend testing as many items as possible to obtain the most accurate total score, especially when measuring change over time is the main priority.¹⁷

Two investigators (MR, BD) will complete the risk of bias assessments for group comparison studies independently of each other, and the third investigator (HLP) will verify their findings and lead the discussion of any identified discrepancies to reach consensus. Similarly, BD and HLP will assess and MR will verify the risk of bias in the SSRDs.

Data synthesis

Group comparison studies assigned a 'low' and 'very low' risk of bias rating, and the SSRDs rated as 'low risk' will be included in the data synthesis. It is anticipated that data may not be appropriate for quantitative synthesis because of the expected heterogeneity of the reviewed studies. Therefore, the majority or the entire report will be a narrative synthesis. However, if a subset or several subsets of the studies provide homogeneous data, we will perform partial meta-analyses of that data. We recognise that physical therapy for children with CP includes a wide variety of interventions. Therefore, we anticipate that data appropriate for meta-analyses may include so-called 'hands-on' therapeutic approaches that involve direct handling of the child by the therapist or 'hands-off,' equipment-based gait training interventions. Even then, we expect to find a high level of heterogeneity of data within each of these two groups of studies.

Confidence in cumulative evidence

The appropriate level of evidence (1 through 5) for each of the group comparison studies will be assigned according to the Oxford Centre for Evidence-Based Medicine.³⁶ The level of evidence of SSRDs will be determined using levels I through V proposed specifically for this type of studies by Romeiser Logan *et al*.³³ Two investigators (HLP, MR) will assign the levels of evidence to group comparison studies independently of each other, and the third investigator (BD) will verify their findings and lead the discussion of any identified discrepancies to reach consensus. Similarly, two investigators (BD, HLP) will assign the levels of evidence to the SSRDs, to be verified by the third investigator (MR) who will lead a discussion of any identified discrepancies to reach consensus.

Patient and public involvement

The development of this systematic review protocol was informed by the authors' clinical practice and academic and research experience gained from working with children with cerebral palsy and their families. No patients will be involved in this systematic review.

Ethics and dissemination

Because this study will involve a systematic review of already published articles, and no primary data collection will take place, no ethical approval is necessary. This systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on June 19, 2020, registration number CRD42020147669. Results will be submitted for publication to a peer-reviewed journal and presented at scientific conferences.

Contributors BD initiated the idea for the systematic review and MR heads the research team. MR and BD developed the selection criteria and completed the initial screening. CLH provided guidance, developed the search strategies and conducted the database searches. MR, BD, HLP and CLH developed the protocol. All four authors participated in the protocol manuscript writing, provided feedback to all, and approved its final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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