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[Intervention Protocol]

Motor interventions initiated prior hospital discharge to prevent neurodevelopmental impairment in preterm infants

Anna Badura[1], Jana Hiekel[2], Agustina Saladino[3], Delfina Murature[3], Mikaela Lenells[4,5], Michelle Fiander[6], Sven Wellmann[1], Matteo Bruschettini[7]

[1]Neonatology, University Children's Hospital Regensburg (KUNO), Hospital St. Hedwig of the Order of St. John, University of Regensburg, Regensburg, Germany. [2]Department of Pediatrics, Faculty of Medicine and University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany. [3]University Italian Hospital, Buenos Aires, Argentina. [4]Women and Children's Health, Karolinska Institute, Stockholm, Sweden. [5]Karolinska University Hospital, Stockholm, Sweden. [6]Cochrane Neonatal Group, Halifax, Canada. [7]Cochrane Sweden, Department of Research, Development, Education and Innovation; Paediatrics, Department of Clinical Sciences Lund, Lund University, Skåne University Hospital, Lund, Sweden

Contact: Matteo Bruschettini, matteo.bruschettini@med.lu.se.

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of motor interventions initiated prior hospital discharge to prevent neurodevelopmental and motor impairment in preterm infants compared to standard care, post-discharge motor interventions, and different modalities of the same motor intervention.

BACKGROUND

Description of the condition

Motor impairment is a prevalent and significant concern among infants born preterm — typically defined as before 37 weeks of gestation [1]. Based on the gestational age, preterms are classified as extremely preterm (less than 28 weeks), very preterm (28 to less than 32 weeks), and moderate to late preterm (32 to 37 weeks). The severity of motor impairment correlates with the degree of prematurity and presence of complications such as intraventricular hemorrhage or periventricular leukomalacia [2, 3, 4].

Within their first month of life, preterm infants demonstrate a poorer quality motor repertoire and less complex postural control than full-term infants [5]. The movement patterns of preterm infants, for example, show less fluidity and variety than those of term infants [6, 7]. Preterm infants are more likely to exhibit abnormal fidgety movements, an early indicator of potential motor impairment, and they often display less complex postural control and rely on fewer strategies to manage posture compared to full-term infants [7, 8, 9, 10].

Around 10% to 15% of preterm infants experience significant motor impairments by age two, including cerebral palsy (CP) [4]. In extremely preterm infants with complications such as severe intraventricular hemorrhage or periventricular leukomalacia, the risk for CP is highest [2]. Even in the absence of major diagnoses like CP, many preterm children exhibit minor neurological dysfunctions including motor difficulties such as poor balance, poor muscle tone regulation, and coordination challenges [11]. Moreover, preterm infants are at risk of developmental coordination disorders affecting both fine and gross motor skills [3]. The presence of motor impairments in preterm infants is closely linked with cognitive development, suggesting that early motor difficulties may serve as early markers for later cognitive challenges [12].

Cognitively, preterm infants typically have lower intelligence quotient (IQ) scores than full-term infants, with an average decrease of one IQ point for each week of early birth [13]. They may suffer from a variety of cognitive impairments and behavioral problems, including attention deficit hyperactivity disorders and autism spectrum disorders, associated with disabilities ranging from mild learning disabilities to severe intellectual disabilities, culminating in lower academic performance in later life [13, 14].

While there is growing evidence that family-centered care, early interventions, and educational support may ameliorate the burden of neurodevelopmental impairments in preterm infants [15], and some evidence that early developmental intervention programs may improve cognitive and motor outcomes during infancy and later in life [16], it is unknown whether motor interventions initiated during a hospital stay positively affect neurodevelopmental outcomes.

Description of the intervention and how it might work

In some neonatal intensive care units (NICUs), physiotherapists are part of the multidisciplinary team and are involved in the assessment and administration of physiotherapeutic interventions in infants born preterm [17]. Physiotherapeutic interventions include habilitative (skill development or improvement) and direct rehabilitative (targeting a specific impairment) proposals which aim to foster maturation of the central nervous system, enrich the environment, and promote better developmental outcomes [15]. It is important to share the goals of the physiotherapeutic program with the infant's family from the outset in order to engage and support them as they cope with the challenges of preterm birth and learn about the risk of developmental delays. Interventions to improve neurodevelopment should be tailored to the infant. To tailor interventions, physiotherapists must choose appropriate, evidence-based interventions and key elements of the intervention (e.g. education or therapeutic modality) and consider methods of delivery for both the infant and the parents [18, 19].

Motor interventions generally refer to therapeutic strategies and activities designed to enhance and support global neurodevelopment and motor abilities in preterm infants [20, 21]. Motor interventions delivered by physiotherapists use various techniques and strategies, such as variations in 24-hour postural care, holding and handling modalities, neuro-sensory and neuro-motor facilitation, and interventions to develop early motor skills (e.g. oromotor competences or midline organization). The use of specific methods, like Bobath and Vojta, have also been reported [20, 21, 22]. All interventions are performed in relation to the age of the child and the possible presence of associated problems.

Motor interventions work through several mechanisms that collectively support the motor and neurophysiological development of the infant. One of the primary mechanisms is the promotion of neuroplasticity. There is evidence that the corticospinal system, a critical pathway for skilled motor behaviors, is active in influencing spinal circuits by the late prenatal period [23, 24]. However, this development can be disrupted by prenatal and postnatal insults. Therapeutic interventions that encourage movement may be crucial for engaging these circuits during their most dynamic phase of plasticity, and may improve movement quality and motor function of preterm children [23, 24]. Motor interventions improve muscle strength and coordination through targeted exercises, and support sensory integration by providing sensory stimulation [25, 26]. Motor interventions support normal movement patterns, and help to prevent secondary complications such as joint contractures and muscle atrophy, which can arise due to prolonged immobility or atypical movement patterns. Additionally, these interventions support somatosensory and proprioceptive perception, both of which are essential for motor control and the ability to adapt movements to different environmental demands. By regulating muscle tone, motor interventions contribute to achieving optimal muscle tension, which is necessary for the development of functional movement skills [26, 27, 28, 29]. Moreover, motor development and psychological development are fundamentally related [30]. Lastly, educating parents on how to support their children's development ensures continued progress and strengthens the parent-child bond [16].

Knowledge about effective motor interventions in preterm infants has increased during the past years. Morgan and colleagues analyzed the effectiveness of motor interventions for infants from birth to two years of age with a diagnosis of, or high risk of developing, CP [21]. They found that early intervention incorporating child-initiated movement (based on motor-learning principles and task specificity), parental education, and environmental modification had a positive effect on motor development. A meta-analysis performed by Hughes and colleagues, investigating interventions that improve motor

development of preterm infants up to 24 months' corrected age, identified interventions with specific motor components as most effective [20]. Khurana and colleagues studied the literature on the efficacy of neonatal therapy starting in the NICU and found that parent-delivered motor interventions were more effective in improving motor and cognitive outcomes in the short-term, and possibly in the long-term, than other interventions [31]. Several randomized controlled studies were conducted on motor interventions initiated prior to hospital discharge, and some of them reported motor outcomes up to two years of age, but efficacy on neurodevelopmental outcome is unclear [28, 32, 33, 34, 35].

Why it is important to do this review

A key competency in providing care in any physical therapy setting is critical appraisal of relevant research and the application of evidence to practice [36]. However, there is debate in the field of early infant development as to how early motor repertoires and neuronal connections can be modified and, if so, at what ages they are most adaptive [33]. Due to different terminology and approaches, there is no consistent definition or understanding of the above techniques and exercises. In practice, physiotherapy is not an established therapy in the care of preterm infants and, in the absence of scientifically validated evidence, the content of motor interventions and the selection of individual exercises are based on the therapist's subjective and experience-based criteria. Although the number of studies on early therapeutic interventions, including motor interventions, is increasing, no systematic review has focused on motor interventions initiated prior hospital discharge to prevent neurodevelopmental impairment in preterm infants.

OBJECTIVES

To assess the benefits and harms of motor interventions initiated prior hospital discharge to prevent neurodevelopmental and motor impairment in preterm infants compared to standard care, post-discharge motor interventions, and different modalities of the same motor intervention.

METHODS

For this protocol, we have followed methodological guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* [37], as well as reporting guidance from PRISMA-P [38]. For the review, we will follow methodological guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* [37], as well as MECIR (Methodological Expectations for Cochrane Intervention Reviews) [39], and report the review following PRISMA [40, 41].

Criteria for considering studies for this review

Types of studies

We plan to include randomized controlled trials (RCTs), quasi-RCTs (trials using strategies of allocation that are not truly random, e.g. allocation by patient ID number) with parallel groups, and cluster-RCTs. We will exclude cross-over randomized trials because they will not be able to report on neurodevelopmental outcomes that develop over time [42]. We will exclude non-randomized cohort studies because they are prone to bias due to confounding by indication or by residual confounding, both of which may influence the results of the studies [43, 44].

Types of participants

We will include studies of preterm infants born at less than 37 weeks' gestational age. We will exclude studies that do not report outcomes for preterm infants separately from those for infants born at term. We will exclude infants with musculoskeletal or congenital malformations or diagnoses of genetic or metabolic syndromes.

Types of interventions

We will define motor interventions as interventions that aim to promote motor development in order to achieve and improve motor control and motor skills in the short and long term. "Motor control is the process by which the brain and nervous system coordinate and regulate muscle activity to produce precise, intentional movements and maintain posture and stability... Motor skills are the abilities that involve the precise movement of muscles with the intent to perform a specific task or achieve a particular goal, encompassing both fine and gross motor skills" [45].

Examples of motor interventions include the following.

- Postural control interventions
- Facilitation of movement and activity-based interventions
- Task-specific motor training
- Parental coaching and parental education about motor interventions
- Techniques aimed at tonus regulation
- Specific interventions such as neurodevelopmental treatment (NDT) — Bobath or Vojta methods

We will exclude studies focused solely on oral, single-sensory, multisensory, positioning, and vestibular interventions because other Cochrane reviews have investigated or will investigate these topics [46, 47, 48, 49].

This review will include studies of motor interventions delivered or initiated during the hospitalization. The intervention must be delivered by physiotherapists, allied health professionals (e.g. nurses), or parents or family members trained by a physiotherapist. We will include studies with interventions of any duration or intensity.

We will include the following comparisons.

- Motor intervention versus standard care (accepted, normal practice in diagnosis, treatment, and management of a particular condition or illness, based on the best available evidence and clinical guidelines)
- Motor interventions initiated/conducted during hospitalization vs. motor interventions initiated/conducted after hospital discharge
- Differing intensity, duration, frequency, or delivery method (e.g. person delivering the intervention) of the same motor intervention

For further information about the characteristics of the interventions and co-interventions, see Investigation of heterogeneity and subgroup analysis.

Outcome measures

Outcome measures are detailed below. We will include studies measuring one or more of the outcomes below, even if the study reports no data for that outcome.

Critical outcomes

The critical outcome is neurodevelopmental impairment assessed at 18 to 24 months corrected age. Neurodevelopmental impairment may be measured by motor or cognitive scales, including but not limited to the following.

- Motor impairment, indicated by a score more than two standard deviations (SDs) below the mean on:
  - Bayley Scales of Infant and Toddler Development (BSID) — Motor Composite Score [50];
  - Griffiths Mental Development Scales — Locomotor subscale [51]; or
  - Peabody Developmental Motor Scales [52].
- Intellectual impairment, indicated by a score more than two SDs below the mean on:
  - BSID Cognitive Composite Score [50]; or
  - Griffiths General Quotient [51, 53].
- CP, defined according to the Gross Motor Function Classification System (GMFCS) [51, 53], as:
  - Severe impairment: non-ambulant CP (GMFCS levels 3–5); or
  - Moderate impairment: ambulatory CP (GMFCS level 2).

We will prioritize the validated measurement instruments above, but will include data regardless of instrument used. If a study reports outcomes using more than one measure or instrument, we will prioritize data from validated instruments.

Important outcomes

The important outcomes of this study will highlight the potential benefits of the intervention, particularly in terms of neurodevelopmental progress, and include the following.

- Short-term outcomes at discharge, including:
  - Total weight gain (grams); and
  - Duration of hospital stay (days).
- Short-term motor impairment, indicated by a score more than two SDs below the mean on:
  - Test of Infant Motor Performance (TIMP), assessed between 34 weeks postmenstrual age and four months corrected age [54]; or
  - Alberta Infant Motor Scale (AIMS), assessed at 0–18 months corrected age [55].
- Parent-reported neurodevelopment progress, indicated by a score more than two SDs below the mean on the Ages and Stages Questionnaire (ASQ-3) at 9, 12, 18, and 24 months corrected age [56].

Search methods for identification of studies

Electronic searches

An Information Specialist (MF) will write searches which will be peer-reviewed by an Information Specialist assigned by the Cochrane Central Editorial Service. We will conduct searches without language or publication status restrictions. We will conduct searches for studies without date limits; we will limit searches for systematic reviews to the past two years. We will search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies (CRS)
- Ovid MEDLINE(R) All, 1946 to Daily Update
- Ovid Embase, 1974 to present
- Ovid Emcare, 1995 to present
- CINAHL, EbscoHost, 1982 to present
- PEDro Physical Therapy Evidence Database (https://pedro.org.au)

A draft MEDLINE strategy is provided in Supplementary material 1 and is preceded by a search narrative [57].

Searching other resources

We will identify study registration records using CENTRAL and by independent searches of the following registers.

- US National Institutes of Health Ongoing Trials Register — ClinicalTrials.gov (clinicaltrials.gov)
- World Health Organization International Clinical Trials Registry Platform (ICTRP; https://trialsearch.who.int/Default.aspx)

We will identify conference abstracts in Embase and CENTRAL and, if accessible, we will search the past three years of the following conferences.

- European Academy of Paediatric Societies (EAPS)
- Pediatric Academic Societies (PAS)
- Perinatal Society of Australia and New Zealand (PSANZ)

We will screen the reference lists of included studies and related systematic reviews for studies not identified by the database searches.

We will search for errata or retractions for included studies published on PubMed and the Retraction Watch Database (https://retractiondatabase.org).

Data collection and analysis

We will collect information regarding the method of randomization, blinding, intervention, stratification, and whether the study was single- or multicenter for each included study. We will note information regarding study participants, including age of gestation at birth, birth weight, and severe complications. We will analyze the clinical outcomes as described in Outcome measures.

In the event we identify and include studies by review authors, two different review authors will independently undertake the following: screening and selection; data extraction; risk of bias assessment; and GRADE assessment.

Selection of studies

We will manage search results in Endnote [58]. We will conduct screening in Covidence [59]; we will use the Cochrane RCT Classifier in Covidence to eliminate known non-RCTs and to tag possible RCTs [60, 61, 62, 63]. In the event the literature searches identify in excess of 4000 references, we may use Cochrane Crowd to further reduce author screening burden. We will report the results of the

RCT Classifier in the review, as well as those for Cochrane Crowd, if used.

Two of four review authors (AB, JH, DM, and AS) will independently screen titles and abstracts followed by the full-text of studies retained during title/abstract screening. We will base decisions for inclusion and exclusion on the Criteria for considering studies for this review. At any point in the screening process, we will resolve disagreements by discussion or by consultation with a third review author (MB). We will present the results of our study selection process in a PRISMA flow diagram [40, 41].

Where there are questions about the data reported in a study, we will attempt to contact study authors for clarification or additional information. If we identify studies in languages not read by review authors, we will first use an online translation service such as Google Translate; if the translation is sufficient, we will use it. If it is insufficient, we will attempt to identify an individual conversant in the language of the report to translate the study.

Data extraction and management

We will extract data using a modified version of the Cochrane Effective Practice and Organisation of Care group data collection checklist [64]. We will pilot the form within the review team using a sample of included studies. Two of four review authors (AB, JH, DM, and AS) will independently extract data for the studies that meet the inclusion criteria. We will resolve disagreements by discussion or in consultation with a third review author (MB).

We will extract the following characteristics for each included study.

- Bibliographic details: authors and other citation information; publication status (published/unpublished)
- Administrative details: study design; year(s) in which study was conducted; pre-registration and/or protocol details; informed consent information (patient level); ethics approval (institutional); study setting — hospital or care unit type; location (geographic); number of centers; lead author contact information
- Conflict or declarations of interest and funding information
- Participant details: number randomized; number lost to follow-up/withdrawn; number analyzed; mean gestational age; gestational age range; mean corrected age; corrected age range; inclusion criteria; exclusion criteria
- Interventions: timing of the intervention such as when it was initiated, frequency, and duration; characteristics of the intervention such as multimodal, unimodal, parent delivered, or therapist delivered
- Comparisons
- Outcomes: as outlined in Outcome measures
- Equity elements (parents/family characteristics) per PROGRESS Plus [65]: place of residence; race/ethnicity/culture/language; occupation; sex; religion; education; socio-economic status; social capital; age; physical or mental disabilities

We will describe ongoing studies identified by our search; we will document available information, such as the primary author, research questions, methods, outcome measures, and an estimate of the anticipated reporting date, in a characteristics of ongoing studies table.

In cases of missing data or uncertainty regarding study methods, we will contact the study authors for clarification. Two of four review authors (AB, JH, DM, and AS) will enter data into Review Manager (RevMan) [66]. We will replace any standard error of the mean (SEM) with the corresponding standard error (SE) [67].

Risk of bias assessment in included studies

We will use the Cochrane risk of bias tool, RoB 2, to assess the risk of bias in randomized trials [68, 69]. We will use an RoB 2 Excel tool to implement RoB 2 (www.riskofbias.info/welcome/rob-2-0-tool). The outcomes that we will assess for each study are those described in Certainty of the evidence assessment.

Two of four review authors (AB, JH, DM, and AS) will conduct independent assessments of risk of bias (low, high, or unclear) of all included studies. We will resolve any discrepancies in judgment through discussion or by consultation with a third review author (SW or MB). We will assess the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* [68].

- Bias arising from the randomization process
- Bias due to deviations from intended interventions (we will assess the effect of assignment to the intervention at baseline, i.e. the 'intention-to-treat effect')
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

To address these types of bias, we will use the signaling questions recommended in RoB 2 and make a judgment using the following options.

- 'Yes': if there is firm evidence that the question was fulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'Probably yes': a judgment was made that the question was fulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'No': if there was firm evidence that the question was unfulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'Probably no': a judgment was made that the question was unfulfilled in the study (i.e. the study was at low or high risk of bias given the direction of the question).
- 'No information': if the study report provided insufficient information to allow any judgment.

We will then use the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias.

- Low risk of bias
- Some concerns
- High risk of bias

This approach will allow the review authors to derive an overall risk of bias rating for each outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judged the trial at low risk of bias for all domains for this result.

- 'Some concerns': we judged the trial to raise some concerns in at least one domain for this result, but not as at high risk of bias for any domain.
- 'High risk of bias': we judged the trial to be at high risk of bias in at least one domain for the result, or we judged the trial to have some concerns for multiple domains such that our confidence in the results is substantially lowered.

If we include cluster-randomized trials, we will use RoB 2 for cluster-randomized trials and follow the guidance in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* [42].

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results using risk ratio (RR) and risk difference (RD) with 95% confidence intervals (CIs). We will calculate the number needed to treat for an additional beneficial outcome (NNTB), or number needed to treat for an additional harmful outcome (NNTH) with 95% CIs if there is a statistically significant reduction (or increase) in RD [67, 70].

Continuous data

For continuous data, we will use the mean difference (MD) when outcomes were measured in the same way across studies. We will use the standardized mean difference (SMD) to combine data from studies that measure the same outcome but use different methods. Where studies report continuous data as median and interquartile range (IQR), and data pass the test of skewness, we will convert the median to mean and estimate the SD as IQR/1.35 [67, 70].

Unit of analysis issues

The unit of analysis will be the participating infant in individually randomized trials; an infant will be considered only once in the analysis. The participating neonatal unit or section of a neonatal unit or hospital will be the unit of analysis in cluster-randomized trials. For cluster-randomized trials, we will abstract information on the study design and unit of analysis for each study, indicating whether clustering of observations is present due to allocation to the intervention at the group level or clustering of individually randomized observations (e.g. infants within clinics). We will abstract available statistical information needed to account for the implications of clustering on the estimation of outcome variances, such as design effects or intracluster correlations (ICCs), and whether the study adjusted results for the correlations in the data. In cases where the study did not account for clustering, we will ensure that appropriate adjustments are made to the effective sample size following Cochrane guidance [70]. Where possible, we will derive the ICC for these adjustments from the study itself or from a similar study. If an appropriate ICC is unavailable, we will conduct sensitivity analyses to investigate the potential effect of clustering, by imputing a range of values of ICC.

If any studies have multiple arms compared against the same control condition that will be included in the same meta-analysis, we will either combine groups to create a single pair-wise comparison or select the pair of interventions that most closely match the definitions given in Types of interventions and exclude the others. We will include the arm where multiple interventions are used and the control group where no specific intervention was introduced. If there are several arms with multiple interventions, we will combine them into one group. If there are several arms with single interventions, we will also combine them and treat them as one comparative group. We will acknowledge this potential selective bias of data used for analysis in the Discussion section of the review.

Dealing with missing data

We intend to carry out analyses on an intention-to-treat basis for all included outcomes. Whenever possible, we will analyze all participants in the treatment group to which they were randomized, regardless of the actual treatment received. If we identify important missing data (in the outcomes) or unclear data, we will request the missing data by contacting the study authors. We will make explicit the assumptions of any methods used to deal with missing data. Where missing data are thought to introduce serious bias (defined as 20% or greater of missing data), we will perform sensitivity analyses to evaluate the impact of missing outcome data.

For missing dichotomous outcomes, we will include participants with incomplete or missing data in the sensitivity analysis by imputing them according to the following scenarios.

- Extreme-case analysis favoring the experimental intervention (best-worst-case scenario): none of the dropouts/participants lost from the experimental arm, but all the dropouts/participants lost from the control arm, experienced the outcome, including all randomized participants in the denominator.
- Extreme-case analysis favoring the control (worst-best-case scenario): all dropouts/participants lost from the experimental arm, but none from the control arm, experienced the outcome, including all randomized participants in the denominator.

The scenarios are constructed with reference to an outcome label that is negative in polarity (e.g. mortality). For the positive equivalent (e.g. survival), the direction in the scenario will be reversed.

For continuous outcomes, we will calculate missing SDs using reported P values or CIs [70]. If this calculation is not possible, we will impute an SD as the highest SD reported in the other studies for the corresponding treatment group and outcome.

We will address the potential impact of missing data on the findings of the review in the Discussion section.

Reporting bias assessment

We will assess reporting bias by comparing the stated primary and secondary outcomes with reported outcomes. Where study protocols are available, we will compare these to the full publications to determine the likelihood of reporting bias. We will document studies using the interventions in an eligible infant population, but not reporting on any of the primary and secondary outcomes, in the characteristics of included studies tables.

We will use funnel plots to screen for publication bias where there are a sufficient number of studies (> 10) reporting the same outcome. If publication bias is suggested by a significant asymmetry of the funnel plot on visual assessment, we will incorporate this in our assessment of certainty of evidence [71]. If our review includes fewer than 10 studies eligible for meta-analysis,

the ability to detect publication bias will be largely diminished, and we will simply note our inability to rule out possible publication bias or small study effects.

Synthesis methods

If we identify multiple studies that we consider to be sufficiently similar, we will perform meta-analysis using RevMan [66]. For categorical outcomes, we will calculate the typical estimates of RR and RD, each with a 95% CI; for continuous outcomes, we will calculate the MD or the SMD, each with a 95% CI.

We will use a random-effects model to combine data, as we expect variation in the underlying treatment effects across studies. Unlike a fixed-effect model, which assumes a single true effect, a random-effects model acknowledges that intervention effects may vary and follow a distribution, typically a normal distribution. This approach considers that differences between study results arise not only from random variation but also from genuine heterogeneity in treatment effects [67].

If there is evidence of clinical heterogeneity, we will try to explain this based on the different study characteristics and subgroup analyses. We will use forest plots to graphically represent the study data.

If we judge meta-analysis to be inappropriate, we will refer to methodological guidance in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* [72], as well as Synthesis Without Meta-analysis (SWiM) reporting guidance [73]. We will create a table with studies ordered by risk of bias, and calculate standardized effect estimates for each study. This table will be modeled on the worked example, Table 12.4.b, in the *Cochrane Handbook for Systematic Reviews of Interventions* [72]. We will use a forest plot to graphically represent the study data.

Investigation of heterogeneity and subgroup analysis

We will describe the clinical diversity and methodological variability of the evidence narratively and in tables. Tables will include data on study characteristics, such as design features, population characteristics, and intervention details. To assess statistical heterogeneity, we will visually inspect forest plots and describe the direction and magnitude of effects and the degree of overlap between CIs. We will also consider the statistics generated in forest plots that measure statistical heterogeneity. We will use the I^2 statistic to quantify inconsistencies among the studies in each analysis. We will also consider the P value from the Chi^2 test to assess if this heterogeneity is significant ($P < 0.1$). If we identify substantial heterogeneity, we will report the finding and explore possible explanatory factors using prespecified subgroup analysis. We will grade the degree of heterogeneity as follows.

- 0% to 40% might not represent important heterogeneity.
- 30% to 60% may represent moderate heterogeneity.
- 50% to 90% may represent substantial heterogeneity.
- More than 75% may represent considerable heterogeneity.

We will use a rough guideline to interpret the value rather than a simple threshold, and our interpretation will take into account the understanding that measures of heterogeneity (I^2 and Tau^2) will be estimated with high uncertainty when the number of studies is small [67]. We will interpret tests for subgroup differences in effects with caution, given the potential for confounding with other study characteristics and the observational nature of the comparisons, as stated in Section 10.11.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* [67]. In particular, subgroup analyses with fewer than five studies per category are unlikely to be adequate to ascertain the valid differences in effects, and we will not highlight them in our results. When subgroup comparisons are possible, we will conduct stratified meta-analysis and a formal statistical test for interaction to examine subgroup differences that could account for effect heterogeneity (e.g. Cochran's Q test or meta-regression) [67, 74]. Given the potential differences in the effectiveness of the intervention related to gestational age and type and length of intervention, we will conduct subgroup comparisons. We plan to carry out the following subgroup analyses of factors that may contribute to heterogeneity in the effects of the intervention.

- Studies in different gestational age groups (< 28 weeks, 28 to < 32 weeks, 32 to < 37 weeks) and birth weight ranges (< 1000 grams, 1000 to < 1500 grams, 1500 to < 2500 grams)
- Evidence of brain injury prior to intervention (absence or presence of grade III or IV intraventricular hemorrhage or cystic periventricular leukomalacia (or both) or an abnormal ultrasound/magnetic resonance image (MRI) before initiation of the intervention)
- Studies completed during inpatient stay versus motor intervention with a post-discharge component
- Studies focused on parent-delivered exercises and educational elements versus those delivered by a therapist
- Studies including co-interventions such as music therapy or multisensory stimulation versus motor intervention alone

We will use the main outcomes (those specified for the summary of findings table) in subgroup analyses if enough studies report the outcomes to support valid subgroup comparisons (at least five studies per subgroup).

Equity-related assessment

We will report any relevant characteristics that are included in the acronym PROGRESS-Plus (place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socio-economic status, social capital, age, sexual orientation, and disability) [65], and whether our neonatal population would be subject to any health inequity in terms of the interventions we will assess.

We anticipate very small differences in terms of financing between high-, middle-, or low-income country settings and populations in terms of the interventions included in our review. However, what might differ between high-, middle-, or low-income countries is the person delivering the intervention. Given that neonates can distinguish who changes diapers or feeds them, they might be better off receiving intervention from their primary caregiver versus a healthcare professional [75]. We will assess this in our review descriptively. In our summary of findings table, we will highlight and present any differences in baseline risks in our neonatal population that might cause disadvantages.

Sensitivity analysis

We will conduct sensitivity analyses to explore the effect of the methodological quality of studies and ascertain whether studies with a high risk of bias (in at least two domains) overestimate the effect of treatment.

Differences in the study design of included studies might also affect the systematic review results. We will perform a sensitivity analysis to compare the effects of motor interventions in truly randomized trials instead of quasi-randomized trials.

We will estimate missing data (i.e. standard deviations) based on change scores or post-intervention values. If we are unable to achieve this, we will contact the study authors to request missing information. However, when we do not receive a response from study authors, we will interpret the results with caution. We will use adjusted estimates if available; otherwise, we will use unadjusted estimates of intervention effects. We will exclude studies with missing data to determine whether their exclusion alters the findings (see Dealing with missing data).

For cluster-randomized trials, we will abstract available statistical information needed to account for the implications of clustering on the estimation of outcome variances, such as design effects or ICCs, and whether the study adjusted results for the correlations in the data. If an appropriate ICC is unavailable, we will conduct sensitivity analyses to investigate the potential effect of clustering, by imputing a range of values of ICC.

Certainty of the evidence assessment

We will use the GRADE approach, as outlined in the GRADE handbook [76], to assess the certainty of evidence for the following Critical outcomes at 18 to 24 months corrected age.

- Motor impairment, indicated by a score more than two standard deviations (SDs) below the mean on:
  - Bayley Scales of Infant and Toddler Development (BSID) — Motor Composite Score [50];
  - Griffiths Mental Development Scales — Locomotor subscale [51]; or
  - Peabody Developmental Motor Scales [52].
- Intellectual impairment, indicated by a score more than two SDs below the mean on:
  - BSID Cognitive Composite Score [50]; or
  - Griffiths General Quotient [51, 53].
- CP, defined according to the Gross Motor Function Classification System (GMFCS) [51, 53], as:
  - Severe impairment: non-ambulant CP (GMFCS levels 3–5); or
  - Moderate impairment: ambulatory CP (GMFCS level 2).

We will include one summary of findings table: motor intervention versus standard care.

Two of four review authors (AB, JH, DM, and AS) will independently assess the certainty of the evidence for each of the outcomes above for each comparison where at least one study is included. The overall RoB 2 assessments will inform our GRADE judgments. We will consider evidence from RCTs as high certainty, downgrading the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We will use GRADEpro GDT to create a summary of findings tables to report the certainty of the evidence [77].

The GRADE approach results in an assessment of the certainty of a body of evidence in one of the following four grades.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

Consumer involvement

This review protocol has been developed with the involvement of consumers, with assistance from the parents of premature children who have required NICU care, and as one review author (ML) is a parent to an extremely preterm child. We expect that this will have made an important contribution to the research question and design, and will be of further importance when interpreting the data, and in the dissemination and translation of the findings.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016170.

Supplementary material 1 Search strategies

ADDITIONAL INFORMATION

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The Methods section of this protocol is based on a standard template used by Cochrane Neonatal.

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

• Sign-off Editor (final editorial decision): Zarko Alfirevic, University of Liverpool

• Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Sue Marcus, Cochrane Editorial Service

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(clinical); and Andréane Lavallée, PhD, Department of Pediatrics, Columbia University Irving Medical Center

Contributions of authors

AB identified the topic of the review, reviewed the literature to inform the protocol, wrote the first draft of the protocol, and reviewed and approved the final version of the protocol.

JH reviewed the literature to inform the protocol, contributed to writing the draft, and reviewed and approved the final version of the protocol.

AS reviewed the literature to inform the protocol, contributed to writing the draft, and reviewed and approved the final version of the protocol.

DM reviewed the literature to inform the protocol, contributed to writing the draft, and reviewed and approved the final version of the protocol.

ML reviewed the literature to inform the protocol, contributed to writing the draft, and reviewed and approved the final version of the protocol.

MF reviewed the literature to inform the protocol, contributed to writing the draft, and reviewed and approved the final version of the protocol.

SW identified the topic of the review, reviewed the literature to inform the protocol, wrote the first draft of the protocol, and reviewed and approved the final version of the protocol.

MB reviewed the literature to inform the protocol, wrote the first draft of the protocol, and reviewed and approved the final version of the protocol.

Declarations of interest

AB has no interests to declare.

JH has no interests to declare.

AS has no interests to declare.

DM has no interests to declare.

ML has no interests to declare.

MF is the Managing Editor and Information Specialist of Cochrane Neonatal; she did not participate in the editorial acceptance of this review.

SW has no interests to declare.

MB is an Associate Editor for Cochrane Neonatal; he had no involvement in the editorial processing of this protocol.

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Registration and protocol

Cochrane approved the proposal of this review in May 2024

Data, code and other materials

As part of the published Cochrane protocol, the following is made available for download for users of the Cochrane Library: search strategies.

As part of the published Cochrane review, the following will be made available for download for users of the Cochrane Library: full search strategies for each database; full citations of each unique report for all studies included, ongoing or awaiting classification, or excluded at full-text screening, in the final review; study data, including study information, study arms, and study results or test data; consensus risk of bias assessments; and analysis data, including overall estimates and settings, subgroup estimates, and individual data rows. Appropriate permissions will be obtained for such use. Analyses and data management will be conducted within Cochrane's authoring tool, RevMan, using the inbuilt computation methods. Template data extraction forms from (59, Excel) will be available from the authors on reasonable request.

Data sharing is not applicable to this article as it is a protocol, so no datasets were generated or analyzed.

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