

Interventions for Central Hypotonia by ICF domain*

*All recommendations in this framework are in favor of the treatment and conditional, due either to the low quality, low number of participants or the focus on related but not specifically meeting all criteria of populations with central hypotonia.

<p>Body Function Outcomes:</p> <ul style="list-style-type: none">-Treadmill training (early stepping and gait)- Active encouragement of developmental milestone gains (motor and sensory-motor function)- AFOs and/or SMOs (gait)	<p>Activities and Participation Outcomes:</p> <ul style="list-style-type: none">-Infant massage (parent-infant interaction, sleep, other)- Early mobility- AFOs and/or SMOs (standing, walking, move around)- Postural Management (sitting, standing, lying, activity)
<p>Body Structure Outcomes:</p> <ul style="list-style-type: none">- Hip surveillance- Postural Management- AFOs and/or SMOs (alignment of body segments)	<p>Environmental Factors Outcomes:</p> <ul style="list-style-type: none">- Walkers and gait trainers- Compression garments- Power mobility- Supported seating system- Standing device

Recommendation 1: ACTIVE MOTOR INTERVENTIONS for infants encourage developmental milestone gains in young children with central hypotonia

FACTOR	DECISION	EXPLANATION
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low	Early reaching, kicking, sitting practice, attaining standing and movement and interventions that are child-active, caregiver delivered, and use coaching have been shown to be effective in infants at risk for cerebral palsy (2 RCTs Morgan et al., 2016 in CP; Heathcock, 2015)
Values and preferences	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	Different weights, kicking and reaching protocols are recommended by different providers. Goal directed, child active interventions with cognitive challenge have shown benefits for Gross and fine motor development and cognitive outcomes in children with CP < 2 years.
Balance of benefits versus disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	Early kicking and reaching promote earlier attainment of developmental milestones. No disadvantages with active motor intervention.
Resource use	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	No resources necessary apart from toys for motivation to move.
Recommendation direction	<input checked="" type="checkbox"/> In favor of the intervention <input type="checkbox"/> Against the intervention	Early, child-active, caregiver delivered interventions coached by a therapist are recommended for all children with motor impairment or developmental delays.
Overall strength of the recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	Active goal directed motor training with cognitive challenge is recommended in children with central hypotonia based on small RCT's in other populations.
References	Morgan et al., 2016; Heathcock, 2015	

Recommendation 2: TUMMY TIME for infants encourage developmental milestone gains in young children with central hypotonia

FACTOR	DECISION	EXPLANATION
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low	Tummy Time intervention has been studied with a single RCT (Wentz 2017) and a case-control study analyzed the use of ankle weights to promote kicking in infants with Down syndrome (Santos, 2014).
Values and preferences	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	Some providers suggest direct floor prone lying, whereas others use supports such as a wedge or soft roll to promote interactions or airway stability.
Balance of benefits versus disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	Tummy Time: Disadvantages are that some adults have difficulty getting on the floor, and pets or other children may make being on the floor undesirable.
Resource use	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	No resources necessary.
Recommendation direction	<input checked="" type="checkbox"/> In favor of the intervention <input type="checkbox"/> Against the intervention	Early, child-active, caregiver delivered interventions coached by a therapist are recommended for all children with motor impairment or developmental delays.
Overall strength of the recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	Although tummy time during supervised play (while child is awake), and other active motor interventions are standard recommendations in pediatric clinical practice and have minimal resource implications, research evidence is limited in children with hypotonia. Note: positioning infants in prone for sleeping is not recommended due to risk of sudden infant death syndrome (SIDS). All recommendations related to use of tummy time are only to be implemented when the child is awake and closely supervised by an adult.
References	Paleg et al., 2018; Wentz, 2017; Santos 2014	

Recommendation 3: INFANT MASSAGE may be used to promote parent child interaction in children with hypotonia. Standardized infant massage can be beneficial for Interpersonal interactions and relationships and domestic life, by promoting parent-infant interaction and improving sleep.

FACTOR	DECISION	EXPLANATION
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low	Three systematic reviews examining effects of massage on infants showed benefits for parent-infant interaction and sleeping. These were not specific to infants with hypotonia. Two low level RCTs in infants with Down syndrome showed effects beyond that expected with maturation on motor development and visual attention.
Values and preferences	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	Significant variability exists between massage protocols, and varied combinations of tactile and kinesthetic elements. Expert consensus was in favor of effleurage delivered by caregivers focusing on parent/infant bonding with careful adjustment to infant responses.
Balance of benefits versus disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	Massage may or may not improve motor development it does not worsen it. Overall, the intervention does more good than harm and the potential impact on caregiver-infant bonding and sleep is important.
Resource use	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	Infant massage for positive results requires training by a therapist and should be caregiver administered. Materials are inexpensive.
Recommendation direction	<input checked="" type="checkbox"/> In favor of the intervention <input type="checkbox"/> Against the intervention	Some, but not a majority of providers recommend implementation of massage (implemented by parents/caregivers) for infants with or without hypotonia, to improve parent-infant interaction and sleeping.
Overall strength of the recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	Based on low quality evidence, tactile and kinesthetic stimulation with massage is recommended in infants with and without hypotonia to improve bonding/interaction and sleeping.
References	Paleg, 2018; Case-Smith, 2013; Alvarez, 2017; Juneau, 2015; Underdown, 2010	

Recommendation 4: TREADMILL TRAINING may be used to promote early onset of walking and improve gait characteristics in children with central hypotonia.

FACTOR	DECISION	EXPLANATION
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low	<p>The quality of evidence is derived from a systematic review of PT/OT interventions for children with hypotonia (Paley, 2018), five systematic reviews of treadmill training for children with motor limitations summarized in an overview (Zwicker & Mayson 2010) and a systematic review specific to children under 6 years of age that included at least 50% children with hypotonia (Valentin-Gudiol 2013). Studies include mainly children with cerebral palsy or Down syndrome. There is overlap in included studies between reviews.</p>
Values and preferences	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	<p>Clinicians support the child with their arms, use overhead support systems (body weight support) and/ or a support walker/gait trainer on the treadmill. Some use light ankle weights. Therapists vary the speed of the treadmill, the schedule and length of sessions.</p>
Balance of benefits versus disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	<p>Treadmill training may facilitate earlier onset of walking and improve stepping and gait patterns. The impact on gross motor development is unclear but no negative effects have been reported. Disadvantages include the difficulty of supporting the child over the treadmill for the session duration, and accessing a treadmill, or a gravity-lessening harness system.</p>
Resource use	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	<p>Treadmill cost varies between models, some families can access treadmills at gyms or community centers. A support walker or gait trainer may be able to achieve similar outcomes. Overhead support systems that remove gravity effects may make the intervention easier to deliver but are costly and may be difficult to access.</p>
Recommendation direction	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	<p>Treadmill training is recommended before and after onset of walking to improve stepping and gait patterns. A gait trainer or walker may be an acceptable substitute in low-resource settings.</p>
Overall strength of recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	<p>Treadmill training has been recommended as standard of care for children with Down syndrome and can reasonably be supported for children with central hypotonia from other causes. Treadmill training can be introduced from 10 months of age.</p>
References	<p>Paley, 2018; Valentin-Gudiol 2011; Zwicker & Mayson, 2010</p>	

Recommendation 5: ANKLE-FOOT ORTHOSES (AFOs) and/or SUPRAMALLEOLAR ORTHOSES (SMOs) may be used to improve foot alignment and gait characteristics for ambulatory children with central hypotonia; in pre-ambulatory children, mixed results prevent recommendation in favor of AFOs and/or SMOs.

FACTOR	DECISION	EXPLANATION
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low	Two systematic reviews, and two lower evidence level RCTs suggest a positive effects of AFOs and/or SMOs on foot alignment and gait in ambulatory children. In pre-ambulatory children, insufficient studies have been performed and results are inconclusive.
Values and preferences	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	<p>Orthotic type is highly variable; type and wear time have not been established.</p> <p>Some use flexible supra malleolar orthoses. One study (Looper & Ulrich 2010;2011) showed that use of AFOs and/or SMOs may negatively impact motor development in pre-ambulatory children with Down syndrome.</p> <p>Two studies recommend lifetime wear for older children and adults with unstable fore, mid and/or hind foot, especially with pronation.(Puszczalowska-Lizis, 2017; Martin, 2004)</p>
Balance of benefits versus disadvantages	<input type="checkbox"/> Benefits outweigh disadvantages <input checked="" type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	<p>If the child is unstable, orthotics may provide proper foot alignment for increased mobility (stepping, walking, running) and exploration while decreasing the risk of injury from malposition or falls.</p> <p>Disadvantages are those of all orthotics: possible weakening of antagonist or small muscle groups and decreased proprioceptive feedback during movement. Use of larger shoes to accommodate AFOs and/or SMOs could increase risk of trips and falls.</p>
Resource use	<input type="checkbox"/> Less resource intensive <input checked="" type="checkbox"/> More resource intensive	<p>AFOs and/or SMOs often require a larger or more specialized shoe than the child typically wears.</p> <p>AFOs and/or SMOs have a limited use-time in developing children due to rapid growth.</p> <p>Some models require skilled orthotists for custom fabrication while others can be bought pre-fabricated.</p> <p>Costs of AFOs and/or SMOs are high and recur in young children due to rapid growth.</p>
Recommendation direction	<input checked="" type="checkbox"/> In favor of the intervention <input checked="" type="checkbox"/> Against the intervention	<p>There is evidence for and against the recommendation.</p> <p>If the child is walking, and if the foot requires additional support for alignment, AFOs and/or SMOs can be beneficial.</p> <p>If the child is pre-ambulatory, low to very low-level evidence exists both in favor and against.</p> <p>Children who are pulling to stand and have good exploratory behavior may be restricted by full-time orthotic device use.</p> <p>Children who lack foot and ankle stability to move and explore in the standing position benefit from orthotic device use.</p>
Overall strength of recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	<p>Wearing of AFOs and/or SMOs during treadmill training may be detrimental.</p> <p>Full-time use of AFOs and/or SMOs may interfere with gross motor development for some children.</p> <p>Children who are unable to move or stand without external support may benefit from orthotic device use.</p>
References	Paleg, et al 2018; Weber & Martin, 2014; Ross & Shore 2011; Looper & Ulrich 2010/2011; Puszczalowska-Lizis, 2017; Martin, 2004	

Recommendation 6: ADAPTIVE EQUIPMENT to modify the environment and allow for increased activity and participation: adaptive seating; walker/gait trainer; stander; power mobility device

FACTOR	DECISION	EXPLANATION
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low	<p>In a systematic review, a small 2 group study found that a supportive seat improved hand use in children with Down syndrome; a single-subject design found that adding a foam support to the seating improved posture in infants with and without hypotonia. (Paleg et al., 2018) A single case design found that a switch adapted ride-on toy car intervention promoted mobility and socialization for a infant with Down syndrome (Logan 2014).</p> <p>Two recent moderate and high-quality SR's on lycra suit use with children with CP provide weak recommendations supporting improvements in postural alignment and gait for trunk and partial body garments, with a strong negative recommendation against full body suits (Almeida et al., 2017; Martins et al., 2015).</p> <p>A review of seating systematic reviews suggested positive but inconclusive benefits of supportive seating for children with a range of diagnoses. (Ryan 2012)</p> <p>One systematic review of gait trainer outcomes suggests positive outcomes for children with cerebral palsy (Paleg & Livingstone, 2016).</p> <p>One systematic review of power mobility interventions (Livingstone & Field 2014) found low level evidence supporting positive effects on development, activity and participation for children.</p> <p>A systematic review of standing interventions found evidence supporting positive body structure and function outcomes for children with a range of diagnoses. (Paleg 2012)</p>
Values and preferences	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	<p>Equipment interventions are widely variable in type of equipment used.</p> <p>Seating interventions range from foam supports in home furniture to specialized supportive seats.</p> <p>Standing supports range from caregiver support to commercial standing frames.</p> <p>Gait trainers range from adult support, supportive harnesses, modified infant walkers, to commercial gait trainers.</p> <p>Power mobility interventions range from inexpensive ride-on toys with/without modifications to specialized devices and power wheelchairs.</p>
Balance of benefits versus disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	<p>Adaptive equipment may facilitate activity and participation by allowing children to maintain position, play, move and explore.</p> <p>Some Items are costly and and are difficult to move from home to childcare or classroom</p> <p>Some equipment requires advanced knowledge for adjustment, maintenance and implementation.</p>
Resource use	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	<p>Adaptive equipment may be costly and resource intensive.</p> <p>Some equipment may be available through recycling or loan programs.</p> <p>Less expensive adaptations may be available but require therapist involvement.</p>
Recommendation direction	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	<p>Promotion of activity and participation outcomes is a goal of pediatric therapy interventions for all young children with delays and functional limitations.</p>
Overall strength of recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	<p>Provision of equipment as an environmental modification can assist children meet activity and participation goals in addition to maintaining body alignment.</p> <p>This recommendation is based mainly on research with other populations related but not identical to central hypotonia.</p>
References	<p>Paleg et al., 2018; Ryan 2012; Paleg & Livingstone 2016; Paleg et al., 2012; Livingstone & Field 2014; Almeida et al., 2017; Martins et al., 2015; Logan 2014</p>	

Recommendation 7: POSTURAL MANAGEMENT - Provide support to facilitate age appropriate activity and participation in natural routines (supported sitting, supported standing) and reduce time spent in asymmetrical lying postures and frog-legged position.

FACTOR	DECISION	EXPLANATION
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very low	<p>Decreased strength, hypermobile joints, increased flexibility and decreased axial tone may lead to delayed motor skills and compensatory strategies to lean on supports [Martin 2007].</p> <p>For preterm children alternating position is beneficial for neurodevelopment, sleep and stress [Vaivre-Douret 2004; Madlinger-Lewis 2014].</p> <p>Postural management promotes alignment and provides appropriate support in sitting and standing and may increase play and activity (Paleg 2016 [Washington 2002]).</p> <p>24-hour postural management has been proposed for children who are displaying asymmetrical and gravity-dependent postures [Pountney 2002]</p>
Values and preferences	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	<p>Postural management varies according to the setting, activity or situation, degree of hypotonia and asymmetry of the child.</p>
Balance of benefits versus disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	<p>There are no disadvantages to promoting symmetric, well supported postures during activity and interactions.</p>
Resource use	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	<p>Postural support requires attention on the part of the caregiver and therapist.</p>
Recommendation direction	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	<p>According to a consensus statement for children with cerebral palsy: Children should start 24-hour postural management programs in lying as soon as appropriate after birth, in sitting from 6 months, and in standing from 12 months (Gericke 2006) or 9 months (Paleg, 2003)</p>
Overall strength of recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	<p>Based on very low level evidence in preterm children, children with related diagnoses, and on ease of implementation, postural support to promote activity is recommended in young children with central hypotonia.</p>
References	<p>Paleg, 2016; Gericke 2006, Pountney 2002; Martin 2005; Martin 2007; Vaivre-Douret, 2004; Madlinger-Lewis, 2014</p>	

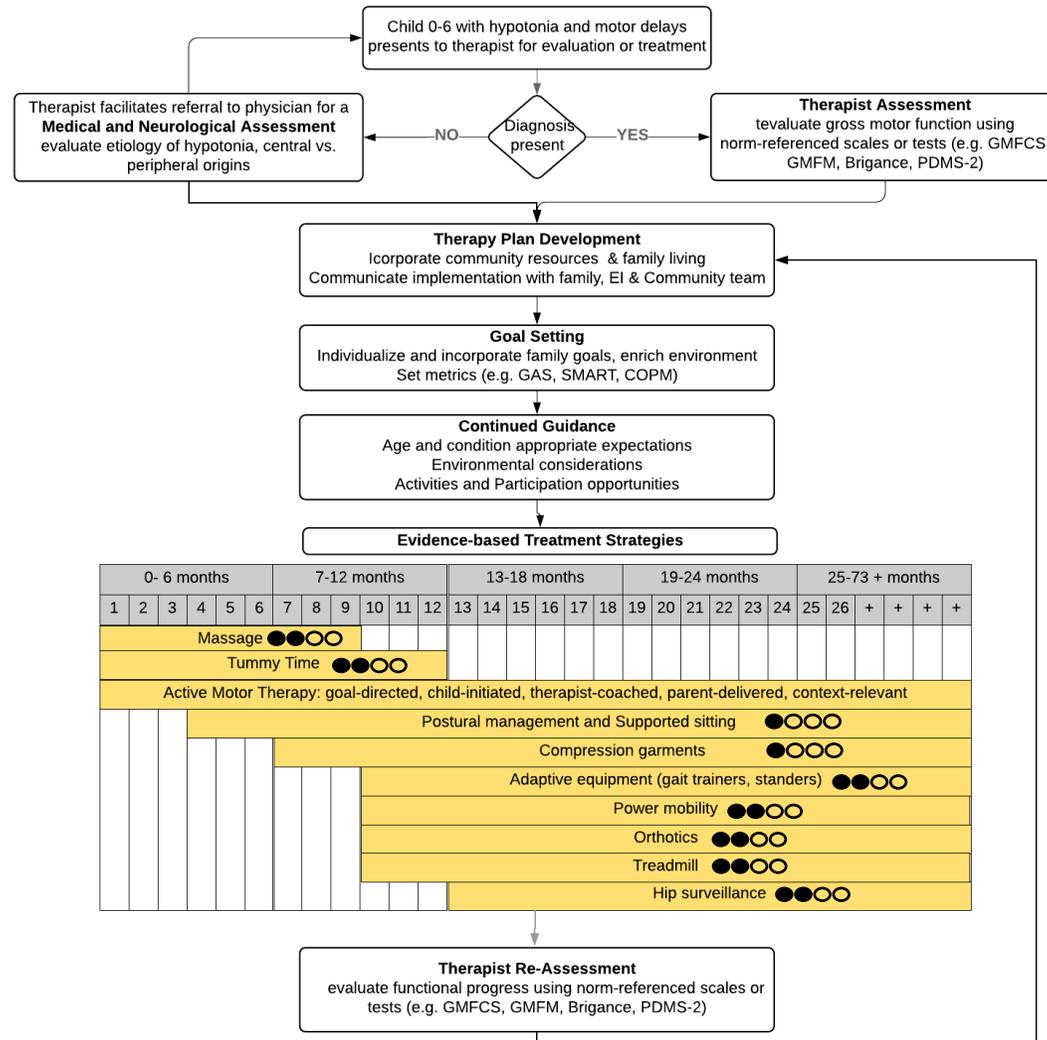
Recommendation 8: HIP SURVEILLANCE to preserve hip health and prevent dislocation by monitoring hip instability or displacement and intervening early to prevent hip dislocation (see AACPDM Hip Surveillance Care Pathway)

FACTOR	DECISION	EXPLANATION
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low	Population studies of children with hypotonia demonstrate increased risk of hip dislocation (up to 7% in children with Down syndrome (DS) [Kelley 2013], and 18% with Joubert [Incecik 2012]). Children with DS have more retroverted and shallower acetabula with reduced coverage of the femoral head [Bulat 2017]. Published recommendations exist in the form of guidelines for children with cerebral palsy and Down syndrome.
Values and preferences	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	Not all clinicians agree that hypotonia without accompanying diagnoses creates an increase risk for hip displacement and dislocation. Guidelines are focused on children who are not walking by age two, or crawling/cruising/pulling to stand by 18 months to 2 years.
Balance of benefits versus disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	The natural history is often progressive, with the typical onset of hypermobility of the hip evolving to habitual dislocation, persistent subluxation, and fixed dislocation, and eventually leading to the loss of independent mobility [Maranho 2018]. Untreated hip dislocation may lead to stiff, painful, dislocated hips. Radiographic and clinical hip surveillance is recommended to prevent dislocation through orthopedic consultation and consideration of timely hip surgery [Kelley 2013]. Mean age for first hip dislocation in DS is 4.6 years [Knight 2011]. Disadvantage is one additional radiograph per year increasing exposure to radiation in the pelvic area.
Resource use	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	Preventative surveillance in the form of regular radiographs is minimally costly. Surgical treatment of hip displacement after limitations to range of motion and dislocation is very costly.
Recommendation direction	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	Classification exists in children with DS with initial phases (0 to 2 y) and dislocation phases (2 to 8) clearly defined.
Overall strength of recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	Based on low quality evidence and international consensus guidelines for related populations, standard hip surveillance is recommended in young children with hypotonia, especially if they are not walking by the age of 2 years.
References	Hägglund 2014, Kelley 2013, Incecik 2012, Knight 2011, Maranho 2018, Bulat 2017	

Recommendation 9: COMPRESSION GARMENTS

FACTOR	DECISION	EXPLANATION
Quality of the evidence	<input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very low	A single case study showed that a compression garment increased child’s ability to roll (Paleg 1999).
Values and preferences	<input type="checkbox"/> No significant variability <input checked="" type="checkbox"/> Significant variability	Compression garments vary from simple low-cost length of neoprene, to high cost custom made vests, shirts and shorts, made from various thickness neoprene, lycra and other circumferential elastic fabrics.
Balance of benefits versus disadvantages	<input checked="" type="checkbox"/> Benefits outweigh disadvantages <input type="checkbox"/> Benefits and disadvantages are balanced <input type="checkbox"/> Disadvantages outweigh benefits	Compression garments may facilitate activity and participation by allowing children to maintain position, play, move and explore. Some families and children report over heating in these garments Care must be taken that the garment is not too tight Some models make diapering and toileting difficult Some models are difficult to don and doff We recommend against models with many extra support panels, which may restrict movement
Resource use	<input checked="" type="checkbox"/> Less resource intensive <input type="checkbox"/> More resource intensive	We recommend starting with least costly options and are cautious about full coverage custom models which require frequent return to the manufacturer for adjustments
Recommendation direction	<input checked="" type="checkbox"/> In favour of the intervention <input type="checkbox"/> Against the intervention	Promotion of activity and participation outcomes is a goal of pediatric therapy interventions for all young children with delays and functional limitations.
Overall strength of the recommendation	<input type="checkbox"/> Strong recommendation <input checked="" type="checkbox"/> Conditional recommendation	Provision of a compression garment as an environmental modification can assist children meet activity and participation goals in addition to maintaining body alignment. Full body suits are not recommended. This recommendation is based mainly on research with other populations related but not identical to central hypotonia.
References	Paleg et al., 2018; Paleg, 1999; Almeida, 2017; Romeo, 2018	

Hypotonia Care Pathway Algorithm



Legend:

Yellow color = GRADE conditional recommendation for all interventions

Evidence levels:

Very Low ●○○○

Low ●●○○

Moderate ●●●○

High ●●●●

AMSTAR for systematic reviews

Intervention	Hypotonia interventions	Orthotics	Treadmill training
Author	Paleg et al 2018	Weber	Valentin- 2017
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	Yes	Yes	Yes
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	Yes	Yes	Yes
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	Yes	Yes	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	Yes	Yes	Yes
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	Yes	No	Yes
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	Yes	Yes	Yes
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	Yes	Yes	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	Yes	Yes	Yes
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I ²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	N/A	N/A	Yes
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	No	No	No
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	No	No	No
Total	8	7	9
Quality: Low = 0-3; Moderate = 4-7; High = 8-11	High	Mod	High