National Institute for Health and Care Excellence

Final

Cerebral palsy in adults

[E] Identifying pain, such as musculoskeletal and gastrointestinal pain

NICE guideline NG119

Evidence reviews

January 2019

Final

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Contents

Techniques for identifying and localising pain in adults with cerebral palsy

Review question

E What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

Introduction

Adults with cerebral palsy may experience pain due to a number of common co-morbidities such as musculo-skeletal and gastro-intestinal problems. In addition adults with cerebral palsy may not be able to communicate their pain and may instead demonstrate pain through changes in behaviours. This review question looks at the available evidence on how to identify the presence, site and severity of pain in adults with cerebral palsy.

PIRO table

Please see Table 1 for a summary of the Population, Index test, Reference standard and Outcome (PIRO) characteristics of this review.

Table 1: Summary of the protocol (PIRO table)

Population	Adults aged 25 years and over with cerebral palsy

Index test	• Self-report pain assessment scales, for example:
	  ○ Faces Pain Scale
	• Observational pain assessment techniques or behavioural scales (including semi-structured interviews of carers or patients when possible), for example:
	  ○ Faces, Legs, Activity, Cry, Consolability Observational Tool
	  ○ Non-communicating Children's Pain Checklist - Revised
	• Physiological measures, for example:
	  ○ Changes in autonomic nervous system
	  ○ Changes in respiratory rate

Reference standard	• Observational or behavioural techniques • Physiological measures

Outcomes	**Critical**
	• Psychometric properties
	  ○ Concurrent validity
	  ○ Internal consistency
	  ○ Inter- or intra-rater reliability
	• Test accuracy:
	  ○ Sensitivity
	  ○ Specificity

For full details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are

described in the review protocol in appendix A and for a full description of the methods see supplementary document C.

GRADE was not used for evidence about clinimetric properties (such as reliability or construct validity), methodological quality was summarised for each publication individually using the consensus-based standards for the selection of health status measurement instruments (COSMIN) checklist for individual studies or the CASP checklist for systematic reviews (see Table 3).

As GRADE is designed only for RCTs and observational studies, a modified version of this tool was used in order to appraise the confidence in the included diagnostic test accuracy evidence. The QUADAS-2 checklist risk of bias and applicability items were used for evaluating the risk of bias and indirectness, respectively, of the studies. The quality assessment of inconsistency and imprecision were adapted to take into account the methodological features of diagnostic studies as described in the footnotes in Table 4 and Table 5.

Declaration of interests were recorded according to NICE's 2014 conflicts of interest policy from May 2016 until April 2018. From April 2018 onwards they were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Interests Register).

Clinical evidence

Included studies

Four cross-sectional studies (number of participants, N=313) were included (Benromano 2017, Boldingh 2004, Collignon 2001 and Jensen 2003). One study examined autonomic pain measures (Benromano 2017), 3 were studies of self-reported pain measures (Benromano 2017, Boldingh 2004 and Jensen 2003) and 2 were studies of observational techniques for measuring pain (Benromano 2017 and Collignon 2001). All studies included adults with cerebral palsy, one study was limited to those with severe learning disability (Collignon 2001) the remainder included those with at moderate, mild or no learning disability (Benromano 2017, Boldingh 2004 and Jensen 2003).

The clinical studies included in this evidence review are summarised in Table 2 and evidence from these is summarised in the clinical evidence profiles in Table 3, Table 4 and Table 5.

See also the literature search strategy in appendix B, study selection flow chart in appendix C, forest plots in appendix E and study evidence tables in appendix D.

Excluded studies

Studies excluded from this systematic review, with reasons for their exclusion, are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2**Error! Reference source not found.** provides a brief summary of the included studies.

Table 2: Summary of included studies

Study	Design	Participants	Index Test	Pain reference standard	Outcomes

Study	Design	Participants	Index Test	Pain reference standard	Outcomes
Benromano 2017	Cross-sectional study	N=18, Adults with cerebral palsy who had no leaning disability (N=5), mild or moderate leaning disability (N=13) Israel	Self-report of pain intensity • Pyramid Pain Scale Observational assessment of pain intensity • Facial expressions • "Freezing" Physiological measures of pain intensity • Galvanic skin response • respiratory rate	Pressure of known intensity	• Validity • Sensitivity • Specificity
Boldingh, 2004	Cross-sectional study	N=164, Adults with cerebral palsy who had no to moderate learning disability (CMMS age of 4 or more) Netherlands	Self-report of pain intensity and location • Pain Assessment Instrument for Cerebral Palsy (PAICP)	Pictures of painful situations, Physio & carer's assessments of typical pain in those situations	• Reliability • Internal consistenc y • Validity
Collignon, 2001	Cross-sectional study	N=62, Adults with cerebral palsy who had severe learning disability France	Observational assessment of pain intensity • 10 item questionnaire	Expert pain ratings of video-recordings Expert decision for analgesic treatment	• Validity • Sensitivity • Specificity
Jensen,2003	Cross-sectional study	N=69, Adults with cerebral palsy who had mild or no learning disability (IQ > 70) USA	Self-report of average pain intensity over the last 24 hours, • 11 & 21 point numeric rating scale • 5 & 16 point verbal rating scale • 6 & 7 point Faces scale	Depressive symptoms (CES-D), pain interference with daily activities (BPI)	• Validity

BPI: brief pain inventory; CES-D: Center for Epidemiological Studies–Depression scale; CMMS: Columbia Mental Maturity Scale; IQ: intelligence quotient; N: number of participants in study; PAICP: Pain Assessment Instrument for Cerebral Palsy; USA: United Sates of America.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this comparison are presented in Table 3, Table 4 and Table 5.

Table 3: Summary of clinical evidence: psychometric properties of autonomic, self-reported and observational pain measures

Study	Pain measure	N	Construct validity[1,6]	Concurrent validity[2,6]	Internal consistency[3,6]	Reliability[4,6]	Quality[5]
Autonomic measures							
Benromano 2017	Heart rate (bpm) (LD group)	13	ρ = 0.12 vs pressure intensity	ρ = 0.11 vs pyramid scale ρ = 0.42* vs FACS	NR	NR	Moderate[7]
Benromano 2017	Heart rate variability (LD group)	13	ρ = -0.06 vs pressure intensity	ρ = -0.15 vs pyramid scale ρ = -0.05 vs FACS	NR	NR	Moderate[7]
Benromano 2017	Pulse amplitude (LD group)	13	ρ = -0.09 vs pressure intensity	ρ = -0.02 vs pyramid scale ρ = 0.41* vs FACS	NR	NR	Moderate[7]
Benromano 2017	Galvanic skin response (LD group)	13	ρ = 0.22 vs pressure intensity	ρ = 0.24 vs pyramid scale ρ = 0.34* vs FACS	NR	NR	Moderate[7]
Self-reported pain intensity measures							
Benromano 2017	Pyramid pain scale (LD group)	13	ρ = 0.63** vs pressure intensity	ρ = 0.49** vs FACS	NR	NR	Moderate[7]
Benromano 2017	Pyramid pain scale (no LD group)	5	ρ = 0.83** vs pressure intensity	NR	NR	NR	Moderate[7]
Boldingh 2004	Pain Assessment Instrument for CP (PAICP) – for usually painful situations	164	ρ = -0.03 to 0.15 vs physio assessment ρ = 0.06 to 0.20 vs carer assessment	NR	α = 0.83	κ = 0.48 to 1.00	Low[8]
Boldingh 2004	Pain Assessment Instrument for CP (PAICP) – for usually non-painful situations	164	ρ = -0.03 to 0.20 vs physio assessment ρ = -0.01 to 0.35** vs carer assessment	NR	α = 0.65	κ = 0.86 to 1.00	Low[8]
Boldingh 2004	Pain Assessment Instrument for CP (PAICP) – for possibly painful situations	164	ρ = 0.29** to 0.52** vs physio assessment ρ = 0.23** to 0.48** vs carer assessment	NR	α = 0.81	κ = 0.86 to 1.00	Low[8]
Jensen 2003	11 point numeric rating scale (NRS-11)	69	ρ = 0.25* vs BPI ρ = 0.30* vs CES-D depression	ρ = 0.87** vs NRS-21 ρ = 0.79** vs VRS-5 ρ = 0.69** vs VRS-16 ρ = 0.71** vs Faces-6 ρ = 0.59** vs Faces-7	NR	NR	Low[10]
Jensen 2003	21 point numeric rating scale (NRS-21)	69	ρ = 0.41** vs BPI ρ = 0.36** vs CES-D depression	ρ = 0.87** vs NRS-11 ρ = 0.82** vs VRS-5 ρ = 0.84** vs VRS-16 ρ = 0.83** vs Faces-6 ρ = 0.81** vs Faces-7	NR	NR	Low[10]
Jensen 2003	5 point verbal rating scale (VRS-5)	69	ρ = 0.29* vs BPI ρ = 0.23 vs CES-D depression	ρ = 0.79** vs NRS-11 ρ = 0.82** vs NRS-21 ρ = 0.85** vs VRS-16 ρ = 0.79** vs Faces-6 ρ = 0.77** vs Faces-7	NR	NR	Low[10]
Jensen	16 point	69	ρ = 0.42**	ρ = 0.69** vs NRS-11	NR	NR	Low[10]

Study	Pain measure	N	Construct validity[1,6]	Concurrent validity[2,6]	Internal consistency[3,6]	Reliability[4,6]	Quality[5]
2003	verbal rating scale (VRS-16)		vs BPI ρ = 0.30* vs CES-D depression	ρ = 0.84** vs NRS-21 ρ = 0.85** vs VRS-5 ρ = 0.82** vs Faces-6 ρ = 0.82** vs Faces-7			
Jensen 2003	6 point Faces Pain Scale (Faces-6)	69	ρ = 0.38** vs BPI ρ = 0.33* vs CES-D depression	ρ = 0.71** vs NRS-11 ρ = 0.83** vs NRS-21 ρ = 0.79** vs VRS-5 ρ = 0.82** vs VRS-16 ρ = 0.85** vs Faces-7	NR	NR	Low[10]
Jensen 2003	7 point Faces Pain Scale (Faces-7)	69	ρ = 0.50** vs BPI ρ = 0.38** vs CES-D depression	ρ = 0.59** vs NRS-11 ρ = 0.81** vs NRS-21 ρ = 0.77** vs VRS-5 ρ = 0.82** vs VRS-16 ρ = 0.85** vs Faces-6	NR	NR	Low[10]
Observational pain intensity measures							
Benromano 2017	Facial Action Coding System (LD group)	13	ρ = 0.42**	ρ = 0.49** vs pyramid scale	NR	ρ = 0.67** to 0.92** inter-rater agreement	Moderate[7]
Benromano 2017	Freezing (LD group)	13	NR	NR	NR	NR	Moderate[7]
Benromano 2017	Freezing (no LD group)	5	NR	NR	NR	NR	Moderate[7]
Collignon 2001	10-item questionnaire (using threshold of 2)	62	κ = 0.47 to 0.64 vs expert panel	NR	α = 0.93	NR	Low[9]
Collignon 2001	10-item questionnaire (using threshold of 6)	62	κ = 0.48 to 0.74 vs expert panel	NR	α = 0.93	NR	Low[9]

** P < 0.05; ** P < 0.01; α: Cronbach's alpha statistic; LD: leaning disability; NR: not reported; κ: Cohen's kappa statistic; FACS: Facial Action Coding System; ρ: Pearson correlation coefficient; physio: physiotherapist*
1 Construct validity – how well does the test measure pain (as measured by the Pearson correlation coefficient or the Cohen's kappa statistic)?
2 Concurrent validity – how does the test compare to other pain measures (as measured by the Pearson correlation coefficient)?
3 Internal consistency – is there general agreement between the different items on the measurement scale (as measured by the Cronbach's alpha statistics)?
4 Reliability – is there agreement between different observers using the same test, or for repeated measurements of a test (as measured by the Cohen's kappa statistic or the Pearson correlation coefficient)?
5 Methodological quality assessed using Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) checklist.
6. Validity, consistency and reliability were rated using the following rule: poor < 0.4, moderate reliability ≥0.4 to 0.6, good >0.6 to 0.8, excellent > 0.8 (Tyson 2014)
7 Pain stimuli were not presented in random order – but were presented from least to most painful.
8 Validity (pain reference standard) based on physiotherapist's and carer's opinion of what situations the participant would find painful.
9 Validity (pain reference standard) based on expert opinion of whether the participants were in pain.
10 Validity (pain reference standard) based on self-reported depression and pain inference.

Table 4: Summary of clinical evidence: diagnostic accuracy of "freezing" (stillness) as a sign of mild or moderate pain, in those with and without learning disability

Study	N	Subgroup	Risk of bias[1]	Inconsistency	Indirectness[3]	Imprecision[4]	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio[5]	Negative likelihood ratio[5]	Quality
1 observational study	13	Learning disability[2]	Serious	Not applicable	Not serious	Serious[7]	0.69 [0.48, 0.86]	0.54 [0.33, 0.73]	1.55	0.57	Low
1 observati	5	No Learning	Serious	Not applicable	Not serious	Very serious[8]	0.80 [0.28,	0.40 [0.05,	1.33	0.50	Very low

Study	N	Subgroup	Risk of bias[1]	Inconsistency	Indirectness[3]	Imprecision[4]	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio[5]	Negative likelihood ratio[5]	Quality
onal study		disability[2]					0.99]	0.85]			

CI: confidence interval; N: number of participants in study
1 Risk of bias evaluated using risk of bias items of QUADAS-2 checklist
2 Learning disability was diagnosed as none, mild or moderate using clinical assessment and standardized testing of intelligence
3 Indirectness was evaluated using the applicability items of QUADAS-2
4 Judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing pain was considered more serious than a false positive - indicating pain when there is none. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9
5 Positive and negative likelihood ratios calculated from sensitivity and specificity estimates
6 Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text) and patient selection; with flow and timing of patient unclear
7 95% CI for sensitivity crosses 0.75
8 95% CI for sensitivity crosses 0.75 and 0.90

Table 5: Summary of clinical evidence: diagnostic accuracy of 10-item observational questionnaire for pain at threshold scores of 2 and 6

Study	N	Threshold	Risk of bias[1]	Inconsistency	Indirectness[3]	Imprecision[4]	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio[5]	Negative likelihood ratio[5]	Quality
1 observational study	50	2[2]	Very serious	Not applicable	Not serious	Very serious[7]	0.88 [0.64, 0.99]	0.73 [0.54, 0.87]	3.24	0.16	Very low
1 observational study	50	6[2]	Very serious	Not applicable	Not serious	Very serious[7]	0.76 [0.50, 0.93]	0.88 [0.72, 0.97]	6.33	0.27	Very low

CI: confidence interval; N: number of participants in study
1 Risk of bias evaluated using risk of bias items of QUADAS-2 checklist
2 The questionnaire score range from 0 to 40, higher scores indicating higher pain
3 Indirectness was evaluated using the applicability items of QUADAS-2
4 Judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing pain was considered more serious than a false positive - indicating pain when there is none. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9
5 Positive and negative likelihood ratios calculated from sensitivity and specificity estimates
6 Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text) and patient selection; with flow and timing of patient unclear
7 95% CI for sensitivity crosses 0.75 and 0.90

See appendix F for the full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no studies were identified which were applicable to this review question.

Excluded studies

No studies were identified which were applicable to this review question.

Summary of studies included in the economic evidence review

No economic evaluations were included in this review.

Economic model

This question was not prioritised for economic modelling as the committee considered that it was unlikely that any recommendation made would place significant additional costs on NHS or PSS budgets.

Resource impact

No unit costs were presented to the committee as these were not prioritised for decision making purposes.

Evidence statements

Autonomic measures of pain intensity

Critical outcomes

Psychometric properties

- Moderate quality evidence from one observational study including 13 people with cerebral palsy and learning disability indicated that autonomic measures were poor indicators of pain intensity. Autonomic measures had poor to moderate agreement with self-reported and observational pain intensity measures.

Test accuracy

- No evidence was found for this outcome

Self-reported pain intensity measures

Critical outcomes

Psychometric properties

- Low quality evidence from one observational study, in which 69 people with cerebral palsy and mild or no learning disability were asked to rate their pain the last 24 hours, suggested good to excellent agreement between self-reported numerical, verbal and faces rating scales. These measures had poor to good agreement with measures of depression and pain interference.
- Moderate quality evidence from one observational study including 13 people with cerebral palsy and learning disability indicated that the self-reported Pyramid pain scale was a good indicator of pain intensity and had moderate agreement with an observational pain measure using facial expressions.
- Low quality evidence from one study including 164 people found the self-reported Pain Assessment Instrument for Cerebral Palsy (PAICP) was a poor to moderate indicator of situations causing hip pain (as judged by carers or physiotherapists). The PAICP had moderate to excellent reliability and good to excellent internal consistency.

Diagnostic test accuracy

- No evidence was found for this outcome

Observational pain intensity measures

Critical outcomes

Psychometric properties

- Moderate quality evidence from one observational study including 13 people with cerebral palsy and learning disability indicated that facial expressions were a moderate indicator of pain intensity and had moderate agreement with the self-reported Pyramid pain scale.
- Low quality evidence from one observational study in 62 people with severe learning disability and cerebral suggested a 10-item observational pain questionnaire was a moderate to good indicator of pain intensity, with excellent internal consistency.

Diagnostic test accuracy

- Low quality evidence from one observational study including 13 people with cerebral palsy and learning disability indicated that freezing (stillness of face and upper body for at least three seconds) had low sensitivity (69%) and specificity (54%) for mild or moderate pain.
- Very low quality evidence from one observational study including 5 people with cerebral palsy without learning disability indicated that freezing (stillness of face and upper body for at least three seconds) had moderate sensitivity (80%) and low specificity (40%) for mild or moderate pain.
- Very low quality evidence came from one observational study in 50 people with severe learning disability and cerebral suggested a 10-item observational pain questionnaire. Using a threshold score of 2, the questionnaire had moderate sensitivity (88%) but low specificity (73%) for an expert's decision to use analgesic treatment. Using a threshold score of 6, the questionnaire had moderate sensitivity (76%) and specificity (88%).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee prioritised the validity, reliability and accuracy of pain measurement scales as the critical outcomes for this question. Because adults with cerebral palsy may have learning or communication difficulties it is important that pain measurement techniques actually measure pain, are reliable and sensitive in order not to miss anyone experiencing pain.

The quality of the evidence

The evidence for validity, reliability and accuracy was of moderate to low quality, using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) criteria. The main issue was the problem of determining how much pain individuals were really experiencing due in part to the ethical problems of inflicting pain in the name of research. The accuracy of pain measurement was only reported in two studies, so it was difficult to judge the usefulness of the various measurement techniques in practice.

The studies also included a mixture of participants, some included adults with cerebral palsy who had mild or no learning disabilities whereas other studies were restricted to adults with cerebral palsy with severe learning disabilities. The committee noted that there was heterogeneity in the study population and its effect on the generalisability of its results. However, since the accuracy of the pain measurement was also the outcome, the committee

agreed that findings were relevant to other adults with cerebral palsy who may experience pain.

Benefits and harms

The committee agreed that people with cerebral palsy may commonly experience chronic pain. Causes could include: increased muscle tone, problems with bones and joints and gastro-oesophageal reflux. If an adult with cerebral palsy is unable to communicate that he or she is in pain, healthcare professionals may not recognise this because distress caused by pain could be mistaken for a symptom of something else, such as anxiety or agitation. The committee therefore wanted to raise awareness to prevent under-identification of pain in adults with cerebral palsy and communication difficulties (with or without learning disabilities).

The committee discussed that the evidence indicated that for adults with cerebral palsy who are able to communicate the numerical, visual analogue and faces pain scales had similarly good reliability and validity and therefore recommended these. Although the use of body maps was not evaluated in the evidence, the committee agreed they would also be a useful way to help localise the source of any pain. These are pictures of a body and people can indicate the place on the picture to show where their pain is coming from which is particularly useful for people who cannot communicate where the pain is located. The committee therefore decided to recommend that any of these tools could be used to help identify and localise pain.

The committee acknowledge that families and carers have valuable insight into the best ways to tell whether an individual was experiencing pain, and this is especially important if the person has communication difficulties. They recommended that this information should be documented in the care plan of adults with cerebral palsy because care staff may change and families may not always be on hand to pass on this knowledge. They also acknowledged that the NICE's guideline on patient experience in adult NHS services provided useful information and advice on how to tailor communication to the needs of individuals and they therefore decided to cross reference to this guideline. For those unable to communicate, the committee agreed that observational and descriptive pain scales would be appropriate and useful.

The committee agreed that people caring for adults with cerebral palsy, particularly for adults who also have communication impairments, would need to have both education in recognising pain and expertise in using a range of pain assessment tools. Having discussions with family about identification of pain as well as training healthcare professionals in how to use assessment tools would improve the recognition of pain and therefore lead to timely management. The committee discussed the fact that the evidence showed that a number of tools had good reliability and validity but they agreed that they did not want to be too specific about one tool since the exact method used would need to be tailored to the individual. It would also depend on the ability of the person with cerebral palsy to communicate and understand the instructions.

The key benefit of the recommendations is to improve identification and localisation of pain to then be able to plan an appropriate strategy to alleviate it.

Cost effectiveness and resource use

The committee noted that no relevant published economic evaluations had been identified for this topic.

As the recommendations largely reflect current best practice, the committee did not believe this would result in any resource impact. The committee agreed that documenting in the care plan on how best to identify pain would improve communication and assessment of pain by all those caring for the person. This could lead to more efficient assessment and reduction in cost. The committee agreed that training of healthcare professionals and family/carers where

appropriate in the use of pain assessment tools, would also be cost effective in terms of time and resources.

Other factors the committee took into account

The committee discussed the use of physiological measures of pain, such as heart rate, but agreed that the evidence was not strong enough to make a useful recommendation either for or against their use. They acknowledged that in their experience acute pain is often associated with an increase in pulse rate and in some cases may be the only sign of pain.

References

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Appendices

Appendix A – Review protocols

Review protocols for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

Table 6: Review protocol for identification of pain

Field (based on PRISMA-P)	Content
Key area in the scope	Identifying pain, such as musculoskeletal and gastrointestinal pain, in adults aged 25 and over with cerebral palsy
Draft review question from the scope (to be deleted in the final version)	What is the most effective sequence of tests to identify causes of pain in an adult with cerebral palsy?
Actual review question	What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?
Type of review question	Diagnostic test accuracy
Objective of the review	The aim of this review is to assess the validity, reliability and accuracy of pain assessment tools in adults with cerebral palsy.
Eligibility criteria – **population**/disease/condition/issue/domain	Adults aged 25 and over with cerebral palsy
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	Self-report pain assessment scales, for example: • Faces Pain Scale Observational pain assessment techniques or behavioural scales (including semi-structured interviews of carers or patients when possible), for example: • Faces, Legs, Activity, Cry, Consolability Observational Tool • Non-communicating Children's Pain Checklist - Revised Physiological measures, for example:

Field (based on PRISMA-P)	Content
	• Changes in autonomic nervous system • Changes in respiratory rate
Eligibility criteria – **comparator(s)**/control or reference (gold) standard	• Observational or behavioural techniques • Physiological measures

Outcomes and prioritisation	Critical outcomes
	• Psychometric properties
	  ○ Concurrent validity
	  ○ Internal consistency
	  ○ Inter- or intra-rater reliability
	• Test accuracy
	  ○ Sensitivity
	  ○ Specificity
	
	The thresholds for clinical usefulness of tests:
	• Sensitivity and specificity (sensitivity will be prioritised as the tests in question):
	  ○ High >90%
	  ○ Moderate 75-90%
	  ○ Low <75%
	• Positive likelihood ratio:
	  ○ Very useful test >10
	  ○ Moderately useful test 5-10
	  ○ Not a useful test <5
	• Negative likelihood ratio:
	  ○ Very useful test <0.1
	  ○ Moderately useful test 0.1 to 0.2
	  ○ Not a useful test>0.2
	• Reliability, validity, or internal consistency
	  ○ Poor < 0.4

Field (based on PRISMA-P)	Content
	○ Moderate reliability ≥0.4 to 0.6 ○ Good >0.6 to 0.8 ○ Excellent > 0.8
Eligibility criteria – **study design**	Only published full text papers - • Systematic reviews of cross-sectional studies/cohort studies • Cohort studies • Cross sectional studies • Validation studies
Other inclusion **exclusion criteria**	None
Proposed sensitivity/**sub-group analysis**, or meta-regression	In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: Population subgroups: ○ GMFCS level I to III vs GMFCS IV to V ○ Level of cognitive impairment ○ Type of cerebral palsy Intervention subgroups: ○ Type of assessment scale: self-report, observational, behavioural ○ Chronic (3 months or more) vs acute pain (less than 3 months)
Selection process – duplicate screening/selection/analysis	A random sample of the references identified in the search will be sifted by a second reviewer. This sample size will be 10% of the total, or 100 studies if the search identifies fewer than 1000 studies. All disagreements in study inclusion will be discussed and resolved between the two reviewers. The senior systematic reviewer or guideline lead will be involved if discrepancies cannot be resolved between the two reviewers.
Data management (software)	Diagnostic analysis was performed using Cochrane Review Manager (RevMan5). STAR was used to sift through the references identified by the search, and for data extraction.
Information sources – databases and dates	Database(s): Embase 1974 to Present, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present. Cochrane Library and Web of Science. Last searched 22/03/2018.

Field (based on PRISMA-P)	Content
Identify if an update	Not an update
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format was used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014 The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' - adapted for diagnostic test accuracy evidence. For the details of this see the methods in supplementary document C.
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual 2014
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details see the methods in supplementary document C.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Paul Eunson in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods in supplementary document C.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.

Field (based on PRISMA-P)	Content
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	Not applicable

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; GMFCS, gross motor function classification system; HTA: Health Technology Assessment; ICF: International Classification of Functioning, Disability and Health; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategies for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

Database: Medline & Embase (Multifile)

Database(s): Embase 1974 to 2018 March 22, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, PsycINFO 1806 to 2018 Week 3 March

Table 7: Last searched on 22 March 2018

#	Searches
1	exp Cerebral Palsy/ use prmz
2	exp cerebral palsy/ use oemezd
3	exp Cerebral Palsy/ use psyh
4	((cerebral or brain or central) adj2 (pal* or paralys#s or pares#s)).tw.
5	cerebral palsy.ti,ab.
6	little? disease.tw.
7	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) adj5 spastic*).tw.
8	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) adj3 ataxi*).tw.
9	or/1-8
10	limit 9 to english language
11	limit 10 to (adult <18 to 64 years> or aged <65+ years>) use oemezd [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,PsycINFO; records were retained]
12	limit 10 to "all adult (19 plus years)" [Limit not valid in Embase,PsycINFO; records were retained]
13	12 use prmz
14	limit 10 to adulthood <18+ years> [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]
15	14 use psyh
16	or/11,13,15
17	exp Visceral Pain/ or exp Pain Threshold/ or exp Pain Management/ or exp Neck Pain/ or exp Pain Measurement/ or exp Pain/ or exp Facial Pain/ or exp Pain Perception/ or exp Pelvic Pain/ or exp Pain, Referred/ or exp Abdominal Pain/ or exp Chronic Pain/ or exp Musculoskeletal Pain/ or exp Low Back Pain/ or exp Chest Pain/ or exp Acute Pain/ or exp Pain Clinics/ or exp Shoulder Pain/ or exp Back Pain/ or exp Facial Expression/ or exp Anger/ or exp Emotions/ or exp Posture/ or exp Prevalence/ or exp "Severity of Illness Index"/ or exp Registries/ or exp Arthralgia/ or exp Disease Progression/ or exp Physicians, Primary Care/ or exp Physician's Role/ or exp Physicians, Family/ or exp Stress, Psychological/ or exp "Quality of Life"/ or exp Perception/ or exp Visual Analog Scale/ or exp Palliative Care/ or exp Behavior Therapy/ or exp Cognitive Therapy/ or exp Adaptation, Psychological/
18	17 use prmz
19	exp limb pain/ or exp low back pain/ or exp heel pain/ or exp Memorial Pain Assessment Card/ or exp chronic inflammatory pain/ or exp visceral pain/ or exp foot pain/ or exp ankle pain/ or exp gastrointestinal pain/ or exp pain/ or exp pressure pain threshold/ or exp jaw pain/ or exp referred pain/ or exp neck pain/ or exp spinal pain/ or exp Faces Pain Scale/ or exp pain parameters/ or exp wrist pain/ or exp "Shoulder Pain and Disability Index"/ or exp pain receptor/ or exp leg pain/ or exp McGill Pain Questionnaire/ or exp pain measurement/ or exp hip pain/ or exp pain clinic/ or exp abdominal pain/ or exp inflammatory pain/ or exp face pain/ or exp skin pain/ or exp upper abdominal pain/ or exp knee pain/ or exp Brief Pain Inventory/ or exp pain severity/ or exp arm pain/ or exp mouth pain/ or exp pain threshold/ or

#	Searches
	exp neuropathic pain/ or exp pain intensity/ or exp chronic pain/ or exp musculoskeletal pain/ or exp pelvic pain/ or exp bone pain/ or exp shoulder pain/ or exp lower abdominal pain/ or exp radicular pain/ or exp musculoskeletal chest pain/ or exp pain assessment/ or exp hand pain/ or exp stomach pain/ or exp phantom pain/ or exp analgesia/ or exp nociception/ or exp prevalence/ or exp facial expression/ or exp anger/ or exp emotion/ or exp body posture/ or exp "severity of illness index"/ or exp register/ or exp arthralgia/ or exp disease course/ or exp general practitioner/ or exp physician attitude/ or exp mental stress/ or exp "quality of life"/ or exp perception/ or exp visual analog scale/ or exp palliative therapy/ or exp cognitive therapy/ or exp behavior therapy/ or exp avoidance behavior/ or exp adaptive behavior/ or exp coping behavior/
20	19 use oemezd
21	exp pain management/ or exp pain perception/ or exp chronic pain/ or exp neuropathic pain/ or exp back pain/ or exp pain measurement/ or exp pain thresholds/ or exp pain/ or exp facial expressions/ or exp anger/ or exp emotions/ or exp posture/ or exp "quality of life"/ or exp "severity (disorders)"/ or exp disease course/ or exp knowledge level/ or exp clinical practice/ or exp primary health care/ or exp therapeutic processes/ or exp physicians/ or exp family physicians/ or exp health personnel attitudes/ or exp health care services/ or exp chronic illness/ or exp home care/ or exp stress reactions/ or exp distress/ or exp stress/ or exp psychological stress/ or exp coping behavior/ or exp rating scales/ or exp psychometrics/ or exp palliative care/ or exp Behavior Therapy/ or exp Cognitive Therapy/ or exp Coping Behavior/ or exp Client Participation/
22	21 use psyh
23	((bod* adj expression*) or (behavio?r* adj change*) or (behavio?r adj therap*) or (cognitive adj therap*) or verbal or non?verbal or pain* or cope* or coping or adapt* or percept* or perceive* or manag* or avoid* or scale* or inventor* or index* or assess* or stress* or palliat*).ti,ab.
24	18 or 20 or 22 or 23
25	16 and 24
26	from 25 keep 1-5000
27	from 25 keep 5001-8151
28	remove duplicates from 26
29	remove duplicates from 27
30	28 or 29
31	conference abstract.pt. use oemezd
32	letter.pt. or LETTER/ use oemezd
33	Letter/ use prmz
34	EDITORIAL/ use prmz
35	editorial.pt. use oemezd
36	NEWS/ use prmz
37	exp HISTORICAL ARTICLE/ use prmz
38	note.pt. use oemezd
39	ANECDOTES AS TOPIC/ use prmz
40	COMMENT/ use prmz
41	CASE REPORT/ use prmz
42	CASE REPORT/ use oemezd
43	CASE STUDY/ use oemezd
44	(letter or comment* or abstracts).ti.
45	or/31-44
46	RANDOMIZED CONTROLLED TRIAL/ use prmz
47	RANDOMIZED CONTROLLED TRIAL/ use oemezd

#	Searches
48	random*.ti,ab.
49	or/46-48
50	45 not 49
51	ANIMALS/ not HUMANS/ use prmz
52	ANIMAL/ not HUMAN/ use oemezd
53	exp ANIMALS, LABORATORY/ use prmz
54	exp ANIMAL EXPERIMENTATION/ use prmz
55	exp MODELS, ANIMAL/ use prmz
56	exp RODENTIA/ use prmz
57	NONHUMAN/ use oemezd
58	exp ANIMAL EXPERIMENT/ use oemezd
59	exp EXPERIMENTAL ANIMAL/ use oemezd
60	ANIMAL MODEL/ use oemezd
61	exp RODENT/ use oemezd
62	(rat or rats or mouse or mice).ti.
63	or/50-62
64	30 not 63

Database: Cochrane Library

Table 8: Last searched on 22 March 2018

ID	Search
#1	MeSH descriptor: [Cerebral Palsy] explode all trees
#2	((cerebral or brain or central) N2 (pal* or paralys?s or pare?s))
#3	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) N5 spastic*)
#4	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) N3 ataxi*)
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Pain] explode all trees
#7	MeSH descriptor: [Facial Expression] explode all trees
#8	MeSH descriptor: [Anger] explode all trees
#9	MeSH descriptor: [Emotions] explode all trees
#10	MeSH descriptor: [Posture] explode all trees
#11	MeSH descriptor: [Prevalence] explode all trees
#12	MeSH descriptor: [Severity of Illness Index] explode all trees
#13	MeSH descriptor: [Registries] explode all trees
#14	MeSH descriptor: [Arthralgia] explode all trees
#15	MeSH descriptor: [Disease Progression] explode all trees
#16	MeSH descriptor: [Physicians, Primary Care] explode all trees
#17	MeSH descriptor: [Physician's Role] explode all trees
#18	MeSH descriptor: [Physicians, Family] explode all trees
#19	MeSH descriptor: [Stress, Psychological] explode all trees
#20	MeSH descriptor: [Quality of Life] explode all trees
#21	MeSH descriptor: [Perception] explode all trees
#22	MeSH descriptor: [Visual Analog Scale] explode all trees
#23	MeSH descriptor: [Palliative Care] explode all trees
#24	MeSH descriptor: [Behavior Therapy] explode all trees

ID	Search
#25	MeSH descriptor: [Cognitive Therapy] explode all trees
#26	MeSH descriptor: [Adaptation, Psychological] explode all trees
#27	bod* expression* or behavio?r* or cognitive or verbal or non?verbal or pain* or cope* or coping or adapt* or percept* or perceive* or manag* or avoid* or scale* or inventor* or index* or assess* or stress* or palliat*
#28	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
#29	#5 and #28

Database: Web of Science

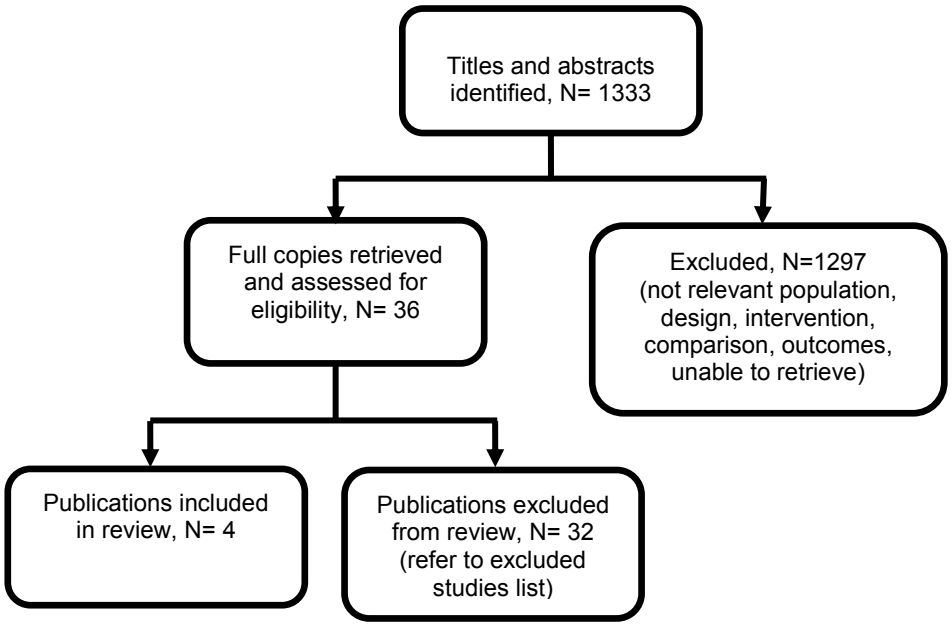
Table 9: Last searched on 22 March 2018

Set	Search
#3	#2 AND #1 AND LANGUAGE: (English)
#2	ts=pain*
#1	ts=cerebral palsy

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

Figure 1: Flow diagram of clinical article selection for the review on pain assessment



Appendix D – Clinical evidence tables

Clinical evidence tables for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

Table 10: Studies included in the evidence review for pain assessment

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Benromano, T., Pick, C. G., Merick, J., Defrin, R., Physiological and behavioral responses to calibrated noxious stimuli among individuals with cerebral palsy and intellectual disability, Pain Medicine (United States), 18, 441-453, 2017 Ref Id 656774 **Country/ies where the study was carried out** Israel **Study type** Cross-sectional study **Aim of the study** To measure behavioural and autonomic nervous system responses to unpleasant stimuli as a way of measuring pain in adults with CP and intellectual disability. **Study dates** Not reported **Source of funding** Not reported	**Sample size** 18 with CP, 15 controls without CP **Characteristics** Age: mean 34.5 (SD 4.9) years GMFCS level I to III vs GMFCS IV to V: not reported Level of cognitive impairment: 9 mild ID, 4 moderate ID, 5 no ID Type of cerebral palsy: 8 Quadriplegia, 2 Hemiplegia, 3 Diplegia, 5 Quadriparesis, **Inclusion Criteria** Participants with mild or moderate ID (based on clinical & standardised assessment) were recruited from a daycare centre, those without ID were recruited from independent residential communities. No other inclusion criteria reported. Controls without CP were recruited from Tel-Aviv University. **Exclusion Criteria** Known acute or chronic pain, bruises, or injuries in the upper mid part of the trapezius muscle region.	**Tests** Pyramid scale (self report) Facial action coding system (FACS) Heart rate Heart rate variability Pulse amplitude Galvanic skin response Freezing	**Methods** Pressure stimuli were delivered, using a hand-held pressure algometer (Algometer type II, Somedic Sales AB, Horby, Sweden). Pressure stimuli of 50, 200, and 400 kPa were chosen based on the ratings of a control group without CP & defined as nonpainful, mildly painful, and moderately painful respectively. The experiment started with a familiarization phase where the person was trained on what to expect with the algometer and how to use the rating scales. Each subject received a total of six pressure stimuli, applied to the upper mid part of the trapezius muscle, alternately to the right and left side. The intensities of the pressure stimuli were: 50, 200, and 400 kPa. Each stimulus rose from a baseline of 0kPa to the destination intensity in 2 seconds, and lasted for 5 seconds. Subjects were asked to rate their pain on the pyramid scale, autonomic responses were measured continuously and facial expressions / behavioural responses were videotaped for rating by two independent observers. The inter-stimulus-interval between sides was 2 minutes and the inter-stimulus interval on the same side was 4 minutes (to avoid carry over stimulation).	**Results** Construct validity - see results summary table in evidence report Concurrent validity - see results summary table in evidence report Internal consistency - not reported Inter or intra-rater reliability - not reported (although autonomic measures should be objective & reliable) Sensitivity & Specificity - reported for freezing	**Limitations** QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear - order of stimuli was not random If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			The order of stimuli was from least to most unpleasant (earlier trials had shown people with ID would withdraw from the experiment if they received the strongest stimulus first).	only	Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk OVERALL ASSESSMENT: moderate quality - due to non-random order of stimuli COSMIN checklist: Internal consistency: NA Reliability: NA Measurement error: fair (unclear if test conditions were similar) Content validity: NA Structural validity: : fair (minor flaws in design of study) Hypotheses testing: NA Cross-cultural validity: NA Criterion validity: NA Responsiveness: NA OVERALL ASSESSMENT: moderate quality
Full citation Boldingh, E. J., Jacobs-van der Bruggen, M. A., Lankhorst, G. J.,	**Sample size** 164 **Characteristics**	**Tests** Pain Assessment Instrument for Cerebral Palsy (PAICP).	**Methods** Reproducibility and construct validity was first assessed in a pilot study with	**Results** Construct validity -	**Limitations** QUADAS 2 checklist Patient selection

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Bouter, L. M., Assessing pain in patients with severe cerebral palsy: development, reliability, and validity of a pain assessment instrument for cerebral palsy, Archives of Physical Medicine & Rehabilitation, 85, 758-66, 2004 Ref Id 347744 **Country/ies where the study was carried out** Netherlands **Study type** Cross-sectional study **Aim of the study** To study the test-retest reproducibility and construct validity of the Pain Assessment Instrument for Cerebral Palsy (PAICP). **Study dates** Not reported **Source of funding** Supported by the Johanna Children Fund and the Dr. W.M. Phelps Foundation for Spastic Children.	Age - mean 36 years (range 16 to 84 years) GMFCS level I to III vs GMFCS IV to V - not reported Level of cognitive impairment - mental age of 4 or greater on the Columbia Mental Maturity Scale Type of cerebral palsy - not reported (reported only as severe CP) **Inclusion Criteria** Adults with severe CP who were unable to walk independently, had a mental age of 4 or above, and were able to use an Faces Pain Scale (FPS). **Exclusion Criteria** Not reported	The PAICP contains drawings of situations, some of which usually produce pain. Patients rate the pain associated with each activity using a 7 point Faces Pain Scale (FPS). Some of the situations are typically not painful (e.g. brushing teeth, listening to music), some are usually painful (wasp sting, squeezing hand in door), other items are possibly painful for people with CP (e.g. sitting in a wheelchair, lying in bed, being lifted from bed, leg physiotherapy)	4 CP patients and 9 healthy children. Construct validity and agreement between the pain scores of the patients and proxies was assessed in 160 patients with severe CP. The construct validity was considered reasonable if the drawings of situations that were usually painful produced a mean score of 3 or higher, and the non-painful situations produced a mean score below 3 on the 7-point FPS scale. The main caregiver and the physiotherapist associated with each patient also predicted their FPS score for each situation.	see results summary table in evidence report Concurrent validity - not reported Internal consistency - see results summary table in evidence report Inter or intra-rater reliability- see results summary table in evidence report Sensitivity & Specificity- not reported	Risk of bias: Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? No If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Questionable - these were pictures of painful situations rather than pain itself Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Moderate risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Moderate risk Flow and timing Risk of bias:

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk OVERALL ASSESSMENT: Low quality - validity based on physio and carers' opinion of what situations the participant would find painful COSMIN checklist: Internal consistency: NA Reliability: poor (small sample size<30) Measurement error: NA Content validity: NA Structural validity: fair (minor flaws in design of study) Hypotheses testing: NA Cross-cultural validity: NA Criterion validity: NA Responsiveness: NA OVERALL ASSESSMENT: low quality
Full citation Collignon,P., Giusiano,B., Validation of a pain evaluation scale for patients with severe cerebral palsy, European Journal of Pain, 5, 433-442, 2001 Ref Id 315925 **Country/ies where the study was carried out** France **Study type** Cross-sectional study **Aim of the study**	**Sample size** 62 for development of questionnaire, 50 for validation **Characteristics** Age - for development of the questionnaire: mean age 16.5 years (range 2 to 33 years). For validation mean age was 20 years (range 6 to 33 years) GMFCS level I to III vs GMFCS IV to V - not reported but all were likely IV or V Level of cognitive impairment - all have severe learning	**Tests** Observational assessment of pain intensity using a 10 item questionnaire (each question rated 0 to 4 for severity): 1: Does the subject usually cry? If so, under what circumstances? Does he/she sometimes cry? If so, for what reasons? 2: Are there usual motor reactions when the subject is manipulated? 3: Does the subject usually	**Methods** An initial 22-item questionnaire by physicians & nurses caring for those with CP was refined to 10 items using multiple component analysis to collapse similar items. For validation the 10-item questionnaire was completed for each person with CP by their usual care giver and by a nurse, by direct observation. Each person with CP was also video-taped in different situations (e.g. washing, during physical therapy during nursing care).	**Results** Construct validity - see results summary table in evidence report Concurrent validity - not reported Internal consistenc	**Limitations** QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
To develop and validate a questionnaire for observational assessment of pain people with severe cerebral palsy. **Study dates** Not reported **Source of funding** Supported by an INSERM grant (CNEP, 92 CN 02).	disability and could not communicate Type of cerebral palsy - severe spastic, dystonic or mixed CP **Inclusion Criteria** Age 2 or older No communication ability (no verbal expression, no communication with signs or symbols) Severe spastic, dystonic or mixed deficiencies such as tetraplegia, triplegia, hemiplegia or diplegia. **Exclusion Criteria** Not reported	smile? If so, is his/her face expressive? 4: Is he/she able to protect his/her face? If so, does he/she tend to do so when touched? 5: Does he/she moan? If so, under what circumstances? 6: Is he/she interested in his/her surroundings? If so, is the interest spontaneous or secondary to stimulation? 7: Is stiffness a problem in everyday life? If so, under what circumstances? (Give examples.) 8: Does he/she communicate with others? If so, does he/she search for contact or must it be elicited? 9: Does he/she present spontaneous motor behaviour? If so, is it voluntary movement, uncoordinated movement, a choreoathetoid syndrome, or reflex movement? If so, is movement occasional or rather permanent agitation? 10: What is his/her usual comfort position? Does he/she tolerate the seated position?	Video recordings were rated independently by three experts into 4 categories: 0: does not seem to suffer (no treatment) 1: pain is caused only by some manipulations (no treatment) 2: seems to suffer (analgesic treatment) 3: pain is certain (analgesic treatment) The sensitivity & specificity of the questionnaire was tested using different cut-off thresholds.	y - see results summary table in evidence report Inter or intra-rater reliability - not reported Sensitivity & Specificity - see results summary table in evidence report	participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? No (but all possible thresholds were examined) Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Unclear (expert opinion on pain) Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Moderate risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk OVERALL ASSESSMENT: Low

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					quality - validity based on expert opinion of whether the participants were in pain or not. COSMIN checklist: Internal consistency: NA Reliability: NA Measurement error: NA Content validity: poor (Not assessed if all items are relevant for the purpose of the application) Structural validity: NA Hypotheses testing: NA Cross-cultural validity: NA Criterion validity: fair (Unclear whether the criterion used can be considered an adequate 'gold standard') Responsiveness: NA OVERALL ASSESSMENT: low quality
Full citation Jensen,M.P., Engel,J.M., McKearnan,K.A., Hoffman,A.J., Validity of pain intensity assessment in persons with cerebral palsy: a comparison of six scales, Journal of Pain, 4, 56-63, 2003 Ref Id 316351 **Country/ies where the study was carried out** USA **Study type** Cross-sectional study **Aim of the study** To determine the relative validity of six pain measures in a sample of persons with CP-related pain. **Study dates** Not reported **Source of funding** This study was supported by a grant "Management of Chronic	**Sample size** 69 **Characteristics** Age - mean 40.61 years (SD 13.05 years) GMFCS level I to III vs GMFCS IV to V: mobility was 17% ambulatory, 62% wheelchair, 7% scooter, 7% crutches, 6% other Level of cognitive impairment - mild or no learning disability (IQ >70) Type of cerebral palsy : spastic 58%, athetoid 13%, hypotonic 3%, mixed 2% **Inclusion Criteria** Participants were recruited from two other ongoing studies. Criteria were: had reported at least one chronic pain problem a primary diagnosis of CP age 18 years or older	**Tests** Self-report of average pain intensity over the last 24 hours using 6 different scales 11 & 21 point numeric rating scales 5 & 16 point verbal rating scales 6 & 7 point Faces scales Depressive Symptoms were measured using the Center for Epidemiological Studies–Depression scale (CES-D) Pain interference was assessed using a modified version of the Pain Interference Scale of the Brief Pain Inventory (BPI)	**Methods** Participants completed each pain intensity measure - but order and timing was not reported.	**Results** Construct validity (does the test measure pain) - pain intensity measures compared with depression & pain interference measures - see outcomes table Concurrent validity (does the test agree	**Limitations** QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Pain in Rehabilitation" (P01 HD/NS33988) from the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke.	mild or no cognitive impairment (IQ > 70) **Exclusion Criteria** Not reported			with other pain measures) - see outcomes table Internal consistency (consistency between measures on the same scale) - not reported Inter or intra-rater reliability - not reported Sensitivity & Specificity - not reported	the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Unclear (depression & pain interference measures) Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Moderate risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear (not reported) Did all participants receive a reference standard? No (a subgroup of 45 were assessed) Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Unclear risk OVERALL ASSESSMENT: Low quality - validity based on self reported depression & pain interference COSMIN checklist: Internal consistency: NA Reliability: NA Measurement error: NA

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Content validity: poor (Unclear whether depression & pain interference measures are good reference standard for pain) Structural validity: NA Hypotheses testing: NA Cross-cultural validity: NA Criterion validity: NA Responsiveness: NA OVERALL ASSESSMENT: low quality

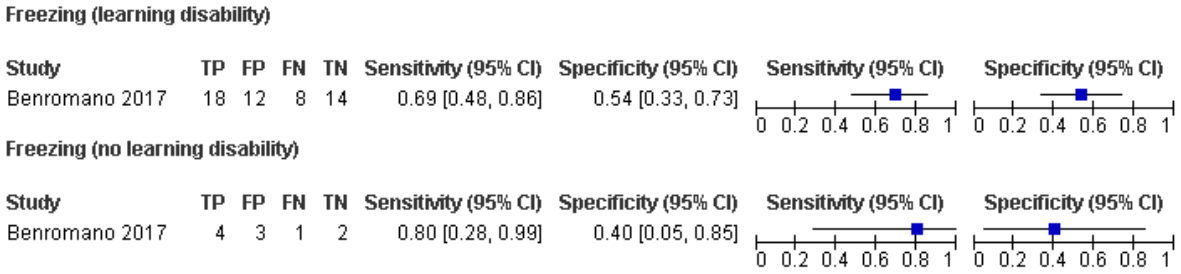
COSMIN: Consensus-based Standards for the selection of health Measurement Instruments; GMFCS: Gross Motor Function Classification System; IQ: intelligence quotient; QUADAS-2: revised tool for the quality assessment of diagnostic accuracy studies; NA: not applicable; SD: standard deviation;

Appendix E – Forest plots

Forest plots for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

Observational pain intensity measures

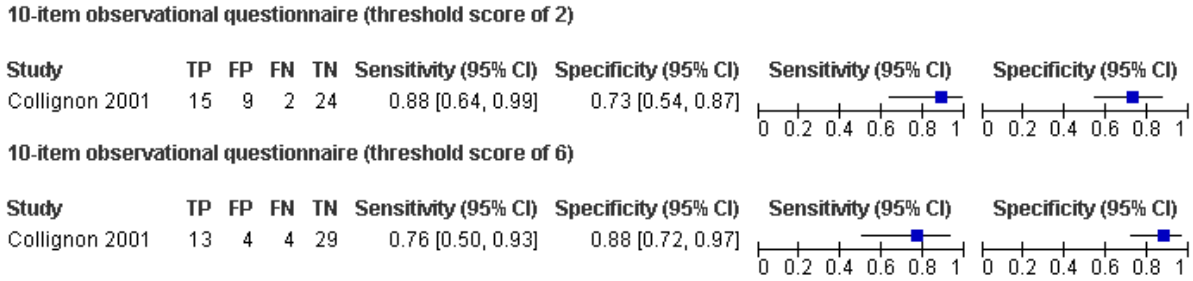
Figure 2: Diagnostic accuracy of freezing (stillness) as a sign of mild or moderate pain, in those with and without learning disability



N=13 for learning disability group and N=5 for no-learning disability group, but each participant was tested with 4 stimuli (2 painful and 2 not).

CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive

Figure 3: Diagnostic accuracy of 10-item observational questionnaire for pain at threshold scores of 2 and 6



CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive

Appendix F – GRADE tables

GRADE tables for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

Table 11: Clinical evidence profile: diagnostic accuracy of "freezing" (stillness) as a sign of mild or moderate pain, in those with and without learning disability

Study	N	Subgroup	Risk of bias[1]	Inconsistency	Indirectness[3]	Imprecision[4]	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio[5]	Negative likelihood ratio[5]	Quality	Importance
1 observational study	13	Learning disability[2]	Serious	Not applicable	Not serious	Serious[7]	0.69 [0.48, 0.86]	0.54 [0.33, 0.73]	1.55	0.57	LOW	CRITICAL
1 observational study	5	No Learning disability[2]	Serious	Not applicable	Not serious	Very serious[8]	0.80 [0.28, 0.99]	0.40 [0.05, 0.85]	1.33	0.50	VERY LOW	CRITICAL

CI: confidence interval; N: number of participants in study
1 Risk of bias evaluated using risk of bias items of QUADAS-2 checklist
2 Learning disability was diagnosed as none, mild or moderate using clinical assessment and standardized testing of intelligence
3 Indirectness was evaluated using the applicability items of QUADAS-2
4 Judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing pain was considered more serious than a false positive - indicating pain when there is none. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9
5 Positive and negative likelihood ratios calculated from sensitivity and specificity estimates
6 Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text) and patient selection; with flow and timing of patient unclear
7 95% CI for sensitivity crosses 0.75
8 95% CI for sensitivity crosses 0.75 and 0.90

Table 12: Clinical evidence profile: diagnostic accuracy of 10-item observational questionnaire for pain at threshold scores of 2 and 6

Study	N	Threshold	Risk of bias[1]	Inconsistency	Indirectness[3]	Imprecision[4]	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio[5]	Negative likelihood ratio[5]	Quality	Importance
1 observational study	50	2[2]	Very serious	Not applicable	Not serious	Very serious[7]	0.88 [0.64, 0.99]	0.73 [0.54, 0.87]	3.24	0.16	VERY LOW	CRITICAL
1 observational study	50	6[2]	Very serious	Not applicable	Not serious	Very serious[7]	0.76 [0.50, 0.93]	0.88 [0.72, 0.97]	6.33	0.27	VERY LOW	CRITICAL

CI: confidence interval; N: number of participants in study
1 Risk of bias evaluated using risk of bias items of QUADAS-2 checklist

2 The questionnaire score range from 0 to 40, higher scores indicating higher pain
3 Indirectness was evaluated using the applicability items of QUADAS-2
4 Judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing pain was considered more serious than a false positive - indicating pain when there is none. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9
5 Positive and negative likelihood ratios calculated from sensitivity and specificity estimates
6 Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text) and patient selection; with flow and timing of patient unclear
7 95% CI for sensitivity crosses 0.75 and 0.90

Appendix G – Economic evidence study selection

Economic evidence study selection for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

No economic evidence was identified for this review.

Appendix H – Economic evidence tables

Economic evidence tables for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

No economic evidence was identified for this review.

Appendix I – Health economic evidence profiles

Health economic evidence profiles for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

No economic evidence was identified for this review.

Appendix J – Health economic analysis

Health economic analysis for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

No economic analysis was included in this review.

Appendix K – Excluded studies

Clinical and economic list of excluded studies for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

Clinical studies

Table 13: Excluded clinical studies for identification of pain

Excluded studies - E.1 What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?	
Study	**Reason for Exclusion**
Andersson, C., Mattsson, E., Adults with cerebral palsy: a survey describing problems, needs, and resources, with special emphasis on locomotion, Developmental Medicine & Child Neurology, 43, 76-82, 2001	Does not evaluate pain assessment methods.
Barney, C., Prowidenza, C., Townley, A., Kingsnorth, S., International collaboration supports improved pain assessment practices for children with cerebral palsy, Journal of Pain, 18, S42-S42, 2017	Abstract only; children only.
Baxter, P., Comorbidities of cerebral palsy need more emphasis - especially pain, Developmental Medicine and Child Neurology, 55, 396-396, 2013	Commentary on another study.
Belew, J., Unraveling the sources of chronic pain in cerebral palsy, Developmental Medicine and Child Neurology, 54, 779-779, 2012	Commentary on another study.
Benrud-Larson, L. M., Wegener, S. T., Chronic pain in neurorehabilitation populations: Prevalence, severity and impact, NeuroRehabilitation, 14, 127-137, 2000	Expert review
Boerlage, A. A., Valkenburg, A. J., Scherder, E. J. A., Steenhof, G., Effing, P., Tibboel, D., van Dijk, M., Prevalence of pain in institutionalized adults with intellectual disabilities: A cross-sectional approach, Research in Developmental Disabilities, 34, 2399-2406, 2013	Only 7% had cerebral palsy.
Boldingh, E. J. K., Jacobs-Van Der Bruggen, M. A. M., Bos, C. F. A., Lankhorst, G. J., Bouter, L. M., Determinants of hip pain in adult patients with severe cerebral palsy, Journal of Pediatric Orthopaedics Part B, 14, 120-125, 2005	Does not evaluate pain assessment methods.
Botura, C. D., Ames, F. Q., Botura, A. C. D., Bersani-Amado, L. E., Bardini, Avsl, Cuman, R. K. N., Pain symptoms in patients with severe cerebral palsy: Prevalence among patients with higher degree of locomotor impairment, Tropical Journal of Pharmaceutical Research, 16, 1431-1436, 2017	Does not evaluate pain assessment methods.
Brunton, L., Hall, S., Passingham, A., Wulff, J., Delitala, R., The prevalence, location, severity, and daily impact of pain reported by youth and young adults with cerebral palsy, Journal of Pediatric Rehabilitation Medicine, 9, 177-183, 2016	Does not evaluate pain assessment methods.
Castle,K., Imms,C., Howie,L., Being in pain: a phenomenological study of young people with cerebral palsy, Developmental Medicine and Child Neurology, 49, 445-449, 2007	Does not evaluate pain assessment methods.
De Knegt, N. C., Pieper, M. J. C., Lobbezoo, F., Schuengel, C., Evenhuis, H. M., Passchier, J., Scherder, E. J. A., Behavioral pain indicators in people with intellectual disabilities: A systematic review, Journal of Pain, 14, 885-896, 2013	Systematic review (outdated - checked for relevant studies)
De Knegt, N., Scherder, E., Pain in adults with intellectual disabilities, Pain, 152, 971-974, 2011	Expert review

Excluded studies - E.1 What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?	
Study	**Reason for Exclusion**
Dudgeon, B. J., Tyler, E. J., Rhodes, L. A., Jensen, M. P., Managing usual and unexpected pain with physical disability: a qualitative analysis, American Journal of Occupational Therapy, 60, 92-103, 2006	Does not evaluate pain assessment methods.
Dudgeon,B.J., Ehde,D.M., Cardenas,D.D., Engel,J.M., Hoffman,A.J., Jensen,M.P., Describing pain with physical disability: narrative interviews and the McGill Pain Questionnaire, Archives of Physical Medicine and Rehabilitation, 86, 109-115, 2005	Does not evaluate pain assessment methods.
Ehde,D.M., Jensen,M.P., Engel,J.M., Turner,J.A., Hoffman,A.J., Cardenas,D.D., Chronic pain secondary to disability: A review, Clinical Journal of Pain, #19, 3-17, 2003	Does not evaluate pain assessment methods.
Engel,J.M., Jensen,M.P., Hoffman,A.J., Kartin,D., Pain in persons with cerebral palsy: extension and cross validation, Archives of Physical Medicine and Rehabilitation, 84, 1125-1128, 2003	Reports prevalence of pain, and its interference with daily activities
Fehlings, D., Pain in cerebral palsy: a neglected comorbidity, Developmental Medicine and Child Neurology, 59, 782-783, 2017	Commentary on another study
Gannotti, M. E., Minter, C. L., Chambers, H. G., Smith, P. A., Tylkowski, C., Self-concept of adults with cerebral palsy, Disability and Rehabilitation, 33, 855-861, 2011	Does not evaluate pain assessment methods.
Giusiano,B., Jimeno,M.T., Collignon,P., Chau,Y., Utilization of neural network in the elaboration of an evaluation scale for pain in cerebral palsy, Methods of Information in Medicine, 34, 498-502, 1995	Describes neural network used for developing an observational pain measure- but its reliability, validity and accuracy are not reported
Hirsh,A.T., Kratz,A.L., Engel,J.M., Jensen,M.P., Survey results of pain treatments in adults with cerebral palsy, American Journal of Physical Medicine and Rehabilitation, 90, 207-216, 2011	Does not evaluate pain assessment methods.
Houlihan, C. M., Walking function, pain, and fatigue in adults with cerebral palsy, Developmental Medicine & Child NeurologyDev Med Child Neurol, 51, 338-9, 2009	Commentary on another study.
Jahnsen, R., Pain hurts 2: changes over time in children and young people with cerebral palsy, Developmental Medicine and Child Neurology, 59, 345-346, 2017	Commentary on another article.
Jahnsen,R., Villien,L., Aamodt,G., Stanghelle,J.K., Holm,I., Musculoskeletal pain in adults with cerebral palsy compared with the general population, Journal of Rehabilitation Medicine, 36, 78-84, 2004	Does not evaluate pain assessment methods.
Paolucci, S., Martinuzzi, A., Scivoletto, G., Smania, N., Solaro, C., Aprile, I., Armando, M., Bergamaschi, R., Berra, E., Berto, G., Carraro, E., Cella, M., Gandolfi, M., Masciullo, M., Molinari, M., Pagliano, E., Pecchioli, C., Roncari, L., Torre, M., Trabucco, E., Values, G., Zerbinati, P., Tamburin, S., Assessing and treating pain associated with stroke, multiple sclerosis, cerebral palsy, spinal cord injury and spasticity Evidence and recommendations from the Italian Consensus Conference on Pain in Neurorehabilitation, European Journal of Physical and Rehabilitation Medicine, 52, 827-840, 2016	Guideline. Checked for relevant studies.
Schwartz,L., Engel,J.M., Jensen,M.P., Pain in persons with cerebral palsy, Archives of Physical Medicine and Rehabilitation, 80, 1243-1246, 1999	Does not evaluate pain assessment methods.
Symons, F. J., Harper, V., Shinde, S. K., Clary, J., Bodfish, J. W., Evaluating a sham-controlled sensory-testing protocol for nonverbal adults with neurodevelopmental disorders: Self-injury and gender effects,	Unclear whether people with CP were included.

Excluded studies - E.1 What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?	
Study	**Reason for Exclusion**
Journal of Pain, 11, 773-781, 2010	
Turk, V., Khattran, S., Kerry, S., Corney, R., Painter, K., Reporting of Health Problems and Pain by Adults with An Intellectual Disability and by their Carers, Journal of Applied Research in Intellectual Disabilities, 25, 155-165, 2012	Does not evaluate pain assessment methods. 3% had CP
Tyler,E.J., Jensen,M.P., Engel,J.M., Schwartz,L., The reliability and validity of pain interference measures in persons with cerebral palsy, Archives of Physical Medicine and Rehabilitation, 83, 236-239, 2002	Earlier publication of the Jensen 2003 study
Tyson, S. F., Brown, P., How to measure pain in neurological conditions? A systematic review of psychometric properties and clinical utility of measurement tools, Clinical Rehabilitation, 28, 669-686, 2014	Systematic review, wider population than our review question - checked for relevant studies (includes Jensen 2003 & Boldingh 2004)
Vogtle,L.K., Pain in adults with cerebral palsy: Impact and solutions, Developmental Medicine and Child Neurology, 51, 113-121, 2009	Expert review.
Weissman-Fogel, I., Roth, A., Natan-Raav, K., Lotan, M., Pain experience of adults with intellectual disabilities - caregiver reports, Journal of Intellectual Disability Research, 59, 914-24, 2015	Does not evaluate pain assessment methods. Unclear how many people with CP were included.
Zwakhalen, S. M. G., Van Dongen, K. A. J., Hamers, J. P. H., Abu-Saad, H. H., Pain assessment in intellectually disabled people: Non-verbal indicators, Journal of Advanced Nursing, 45, 236-245, 2004	Unclear what proportion had CP

CP: cerebral palsy.

Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question E: What is the value of self-report and observational techniques for providing a standardised way of identifying and localising pain in adults with cerebral palsy?

No research recommendation was made for this review.