Economic evaluation and cost of interventions for cerebral palsy: a systematic review

SOPHY T F SHIH[1] | UTSANA TONMUKAYAKUL[1] | CHRISTINE IMMS[2] | DINAH REDDIHOUGH[3,4] | H KERR GRAHAM[5] | LIZ COX[6] | ROB CARTER[1]

1 Deakin Health Economics, Centre for Population Health Research, Faculty of Health, Deakin University, Geelong, Victoria; **2** Centre for Disability and Development Research, Australian Catholic University, Fitzroy, Victoria; **3** Murdoch Children's Research Institute, Parkville, Victoria; **4** The University of Melbourne, Parkville, Victoria; **5** Royal Children's Hospital, Parkville, Victoria; **6** Victorian Managed Insurance Authority, Melbourne, Victoria, Australia.

Correspondence to Sophy T F Shih at Deakin Health Economics, Centre for Population Health Research, Faculty of Health, Deakin University, 221 Burwood Highway, Burwood, Vic. 3125, Australia. E-mail: sophy.shih@deakin.edu.au

PUBLICATION DATA
Accepted for publication 20th November 2017.
Published online

ABBREVIATIONS

CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
ICER	Incremental cost-effectiveness ratio
ITB	Intrathecal baclofen
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial

AIM Economic appraisal can help guide policy-making for purchasing decisions, and treatment and management algorithms for health interventions. We conducted a systematic review of economic studies in cerebral palsy (CP) to inform future research.
METHOD Economic studies published since 1970 were identified from seven databases. Two reviewers independently screened abstracts and extracted data following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Any discrepancies were resolved by discussion.
RESULTS Of 980 identified references, 115 were included for full-text assessment. Thirteen articles met standard criteria for a full economic evaluation, two as partial economic evaluations, and 18 as cost studies. Six were full economic evaluations alongside clinical studies or randomized controlled trials, whereas seven involved modelling simulations. The economic case for administration of magnesium sulfate for imminent preterm birth is compelling, achieving both health gain and cost savings. Current literature suggests intrathecal baclofen therapy and botulinum toxin injection are cost-effective, but stronger evidence for long-term effects is needed. Lifestyle and web-based interventions are inexpensive, but broader measurement of outcomes is required.
INTERPRETATION Prevention of CP would avoid significant economic burden. Some treatments and interventions have been shown to be cost-effective, although stronger evidence of clinical effectiveness is needed.

Cerebral palsy (CP) describes a group of developmental disorders of movement and posture, causing activity restriction or disability attributed to disturbances occurring in the fetal or infant brain. The motor impairment may be accompanied by a seizure disorder and by impairment of sensation, cognition, communication and/or behaviour, and by secondary musculoskeletal problems.[1] CP has a prevalence of approximately 1 in 500 neonates, with 17 million people affected worldwide.[2] The overall prevalence of CP in high-income countries is 2.11 per 1000 live births,[3] and 2.0 to 2.8 per 1000 live births in low- and middle-income countries.[4] In Australia, after a long period of stable prevalence at 2 to 2.5 per 1000 live births, the rate of CP declined to 1.4 to 2.1 per 1000 live births between 2007 and 2009.[5] The downward trend is particularly evident in infants born extremely preterm. The severity and complexity of CP has also declined. The CP registers in some Australian states have estimated the current CP prevalence to be less than 1.5 per 1000 live births.[6]

The precise aetiology of CP is still unclear. Risk factors for CP include preterm birth, multiple pregnancy, intra-amniotic infection, perinatal inflammation, low maternal thyroid hormone levels, perinatal asphyxia, placenta abnormalities, fetal growth retardation, and neonatal hyperbilirubinaemia. While CP involves damage to the central nervous system, clinical symptoms of CP are predominantly observed in the musculoskeletal system. In addition, 31% of children with CP born between 1993 and 2006 had epilepsy, 5% were blind, 2% were deaf, and 44% had intellectual impairment.[7]

CP is a lifelong condition, with profound impacts on the individuals, as well as their family. Mothers of children with CP have poorer mental and physical health outcomes than mothers of children with typical development.[8,9] From a broader perspective, CP also significantly affects education and welfare systems. Given the burden and impact of CP, improvements in our knowledge base to guide treatment and prevention is crucial. While clinical research has progressed our understanding of risk factors

and efficacy, our knowledge of cost-effectiveness and how best to utilize available budgets is poorly documented.

We conducted a systematic review to provide information on the economic aspects of CP that have been researched and to identify the strengths/weaknesses and gaps in the current economic research. We aim to address the cost and cost-effectiveness of interventions focusing on CP for individuals from the pre-/perinatal period through to adolescence in studies reporting clinical investigations and/or modelling simulations. This study is, to our knowledge, the first systematic review on economic evidence for CP-specific interventions.

METHOD

A systematic review was conducted, following the Cochrane Systematic Review and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, to identify economic studies on interventions for children with CP.[10,11]

Search strategy

Seven electronic databases (Ovid MEDLINE, Embase, CINHAL, PsycINFO, Econlit, Health Economic Evaluation Database, and NHS Economic Evaluation Database in the Cochrane Library) were searched with the following search terms: (1) 'cerebral palsy'; (2) 'health care costs' and 'cost analysis'; and (3) 'economic evaluation' (including 'cost-effectiveness analysis' and 'cost-benefit analysis'). The search strategies for various databases are documented in Table I. The literature search was restricted to articles written in English and published from 1970 to the present. A manual search of references in selected articles was also carried out to identify additional relevant studies. The search of published studies was performed in December 2015 and updated in April 2017.

Table I: Search strategies for various databases

Database	Search terms
Ovid Medline	
1	"cerebral palsy".sh
2	cost*.ab. or "costs and cost analysis".sh. or "cost benefit analys*".ab. or "cost-benefit analysis".sh. or "health care costs".xs
3	1 and 2
Embase	
#1	'cerebral palsy':ab,ti
#2	'cost':ab,ti
#3	'cost effectiveness analysis':ab,ti
#4	'cost benefit analysis':ab,ti
#5	'health care costs':ab,ti
#6	#2 OR #3 OR #4 OR #5
#7	#1 AND #6
CINAHL, PsycINFO, HEED, EcoLit databases	
S1	MJ cerebral palsy or TI cerebral palsy or AB cerebral palsy
S2	TX (cost effective analysis or cost effective* or cost benefit analysis or economic evaluation)
S3	TX (randomized controlled trial or rct)
S4	S1 AND S2 AND S3

Sh, subheading; ab, abstract; xs, exploded subheading; ti, title; MJ, word in major subject healding; S, search.

What this paper adds

- Cost-effectiveness evidence shows prevention is the most significant strategy.
- Some treatments are cost-effective, but stronger evidence for long-term effectiveness is required.
- Comparison of treatment costs is challenging owing to variations in methodologies and varying clinical indications.

Inclusion and exclusion criteria

Two reviewers (STFS and UT) independently screened all titles and abstracts identified. Publications meeting the inclusion criteria were included for full-text assessment. Discrepancies between two screening results were discussed (STFS, UT, RC) and resolved. Inclusion for full-text assessment were those articles reporting costs, cost estimates, cost-effectiveness, cost–benefit, or economic evaluation in CP. Studies that only reported CP as one of the outcomes measured, rather than investigating interventions for CP prevention or treatment, were excluded. For example, a wide range of perinatal interventions to prevent adverse birth outcomes have been studied. The studies that included CP as one of the outcomes with less than 10% of cases reported were excluded from the current review.

Economic evaluation studies were appraised against the checklist criteria for assessing economic evaluation set by Drummond et al.[12] The checklist of Drummond et al. consists of 10 important areas: (1) well-defined questions; (2) comprehensive description of the competing alternatives; (3) established effectiveness; (4) identification of relevant costs and consequences; (5) appropriate measurement of costs and consequences; (6) credible valuation of costs and consequences; (7) costs and consequences adjusted for timing; (8) incremental analysis; (9) uncertainty analysis; (10) discussion of issues of concern to users.

Data extraction

A data extraction template was developed and utilized for each of the studies selected for full-text analysis. Extracted information included author names, year of publication, country of study, aim of study, study type, population included, intervention studied, comparison group, time horizon of study, currency and reference year, main results, and comments for discussion. Data were extracted independently by two reviewers (STFS and UT). Discrepancies on extracted data were cross-checked and discussed, with final decisions agreed between STFS, UT, and RC.

Outcome measures

Two outcome measures were targeted in the review: 'cost' (defined according to the method used in the study, e.g. total cost, per case, per episode, lifetime, etc.) and the 'cost-effectiveness ratio' (e.g. incremental cost-effectiveness ratio [ICER]). Costs were normally reported as costs of specific treatment for CP. Health economics studies presenting the burden of disease or cost of illness related to CP were excluded from the present paper and reported elsewhere.[13] The focus of the present paper was to provide a value judgement of efficiency for interventions targeting

CP, whereas the burden of disease or cost of illness studies presented a description of the magnitude of the condition or impact of the problem without enough information to make value judgements. Although studies reporting cost of specific treatment or therapy do not assist in making a value judgement of efficiency, they were included in the present paper as they provided information about budget implications of interventions for CP. For the purposes of this review, arguable assumptions made in included studies, if any, were also recorded to flag variations between studies.

RESULTS

There were 980 references identified from the electronic databases. After removal of duplicates, 706 titles and abstracts were screened. Based on our inclusion criteria, 115 articles were included for full-text assessment. Of these, 15 articles met the criteria of economic evaluation and 18 publications reported cost of treatment. The PRISMA flowchart, demonstrating the identification, screening, eligibility, and inclusion of studies, is shown in Figure 1.

The 15 included articles reported economic evaluation results of ICER for the following interventions: prevention of CP (*n*=4, including one conference abstract);[14–17] botulinum toxin A (BoNT-A) injection (*n*=4, including one conference abstract);[18–21] intrathecal baclofen (ITB) therapy (*n*=3);[22–24] functional electrical stimulation (*n*=1);[25] proximal femoral hardware retention (*n*=1);[26] web-based home program (*n*=1);[27] and lifestyle intervention (*n*=1).[28] Seven

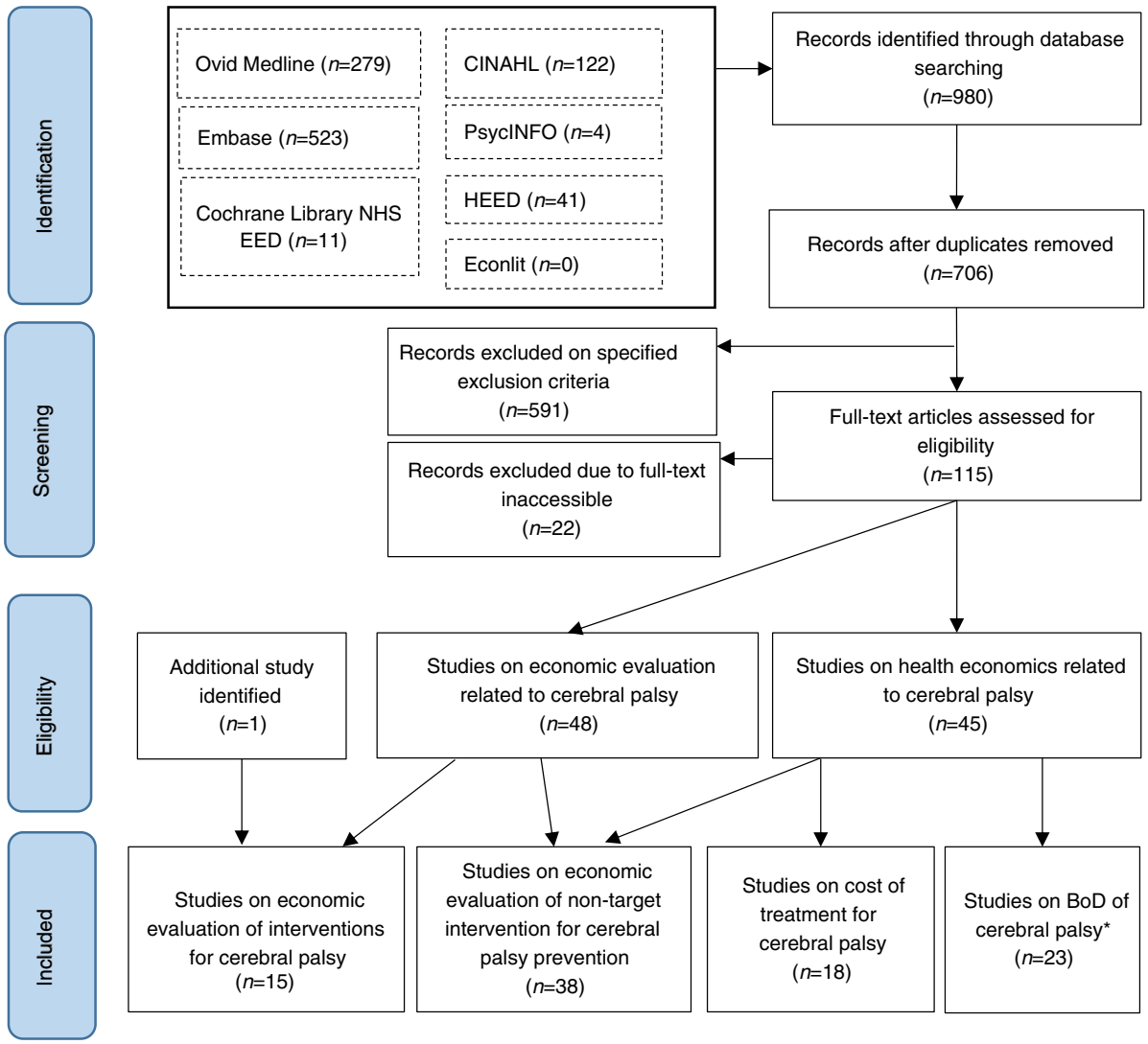

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. NHS, National Health Service; EED, Economic Evaluation Database; HEED, Health Economic Evaluations Database; BoD, burden of disease.

of these economic evaluations were conducted by a modelling approach, whereas six were economic evaluations alongside clinical studies or randomized controlled trials (RCTs). The results of the data extractions from the economic evaluation studies are listed in Table II. Two studies were classified as partial economic evaluations (i.e. functional electrical stimulation and proximal femoral hardware retention) as either no comparison group data was presented or no comparison of outcome and cost were carried out.

There were 18 publications that reported on the costs of treatment and therapy in 15 studies, either as part of a clinical study assessing effectiveness, or as a dedicated economic study. Among these, six studies were cost analyses or budget impact analyses of BoNT-A; four involved ITB therapy; four were cost studies of various surgical procedures; two were assessments of gait analysis; and two studies focused on community-based care and a specialized seating delivery model. Details of included economic evaluation and cost analysis studies are discussed blow.

Economic evaluation studies on prevention of CP

Magnesium sulfate

Administration of magnesium sulfate in females at risk of preterm birth to prevent CP is the most promising intervention of those studied to date. Two decision-analytic modelling studies were carried out by Cahill et al. and Bickford et al. to assess the cost-effectiveness of this intervention.[14,16] Both studies modelled the cost and outcome for a lifetime horizon and were undertaken from both the 'health system' perspective to account for resources incurred in the health care sector, including out-of-pocket costs to the individuals, and the 'societal' perspectives to capture a broader range of impacts.

In the study by Cahill et al.,[16] cost was estimated in US dollars and outcomes were reported as quality-adjusted life-year (QALY). The strategies were also compared in terms of 'cases prevented', 'neonatal or infant deaths', and cost-effectiveness ratios. In the study by Bickford et al.,[14] CP was the only neonatal outcome included in the models and all costs were presented in 2011 Canadian dollars (CAN$). Data from four RCTs were pooled to obtain the probabilities of CP of various severities for the Canadian study.[29–32]

For imminent preterm birth, use of magnesium sulfate was a dominant strategy that is both less costly and more effective than the alternative of no treatment from both the 'health system perspective' and the broader 'societal perspective'.[14] The broader perspective included productivity costs, such as all costs associated with lost labour market productivity for adults with CP, and social costs consisting of all costs associated with specialized education, specialized housing, and lost labour market productivity for primary care providers of children with CP.

For threatened preterm birth, the intervention was dominant from the 'societal' perspective and cost-effective from a 'health system' perspective. From the narrower 'health system' perspective, the model predicted an ICER of CAN $2083 per QALY gained and CAN$28 755 per CP averted. With the decision threshold for cost-effectiveness of '$50 000 per QALY' applied in countries like Australia, the UK, and Canada, a result of CAN$2000 per QALY would suggest strong cost-effectiveness.

The study of Cahill et al. also suggested that, compared with no treatment, magnesium sulfate was the dominant strategy (saving costs and gaining more health benefits) when given to females with preterm, premature rupture of membranes, as well as females at risk of delivery before 28 weeks' gestation.[16] However, the intervention was not cost-effective when the risk reduction in moderate-to-severe CP by the magnesium treatment was less than 14%.

Other preventative interventions for CP

One study reported a trial-based economic evaluation of two fetal surveillance strategies focused specifically on the prevention of CP.[17] The trial results indicated a reduction of CP cases through the surveillance strategies of cardiotocography plus ST-segment waveform analysis of the fetal electrocardiogram versus cardiotocography alone. Without a common metric like QALYs, this result is limited in informing the 'value-for-money' of surveillance per se, but is useful for decisions around technical efficiency (i.e. how to offer surveillance to whom with what modality, if a decision is to be made to offer fetal surveillance). We are unable to conclude whether or not this intervention is cost-effective by the threshold of $50 000 per QALY. However, fetal surveillance is significantly less cost-effective by the ICER of €167 854 per one CP case prevented compared with the ICER of CAN$28 755 per CP averted by magnesium intervention.

Economic evaluation studies on treatment for CP

BoNT-A injection

Three studies have assessed the cost-effectiveness of BoNT-A injection in the management of spasticity, but they demonstrate inconsistent results.[19–21] In a modelled evaluation in the Australian setting, conducted as part of an application to the Pharmaceutical Benefits Advisory Committee for drug listing, the case is based on equivalent efficacy of BoNT-A injection and serial casting. The effects of BoNT-A lasted longer and therefore it was regarded as the preferred treatment.[21] The efficacy of the treatment was modelled from RCTs including Australian patients.[33,34] A cost consequences analysis was undertaken in which the costs and consequences of treatment were presented separately and only the direct medical costs were included. The additional cost for BoNT-A injection, discounted at 5% annually, was 793 Australian dollars (AUD $) for patients with hemiplegia and AUD$867 for diplegia, over a treatment interval of 3.7 years. The study concluded that the additional costs associated with BoNT-A over and above serial casting treatment were modest and could be offset by indirect costs (e.g. travel costs) if analysed from a societal perspective.

Table II: Data extraction from studies reporting an economic evaluation of interventions for cerebral palsy (CP)

References	Country	Aim	Study type	Time horizon	Population	Comparison	Population	Study results	Comments
Magnesium sulfate									
Bickford et al.[14]	Canada	To assess the cost-effectiveness of administering magnesium sulfate to patients in whom PTB at <32wks' gestation	Decision-tree models and probabilistic sensitivity analyses using TreeAge	Life expectancies at birth	Magnesium sulfate for fetal neuroprotection	No treatment	Patients in whom PTB at <32+0wks' gestation is imminent or threatened	From a health system and a societal perspective respectively, savings of CAN$2242 and CAN $112,602 are obtained for each QALY gained Savings of CAN$30,942 and CAN$1,554,198 is obtained for each case of CP averted when magnesium sulfate is administered to patients in whom PTB is imminent From a health system perspective and a societal perspective respectively, a cost of CAN$2083 is incurred and savings of CAN$108,277 is obtained for each QALY gained and a cost of CAN$28,755 is incurred and a saving of CAN$1,494,500 is obtained for each case of CP averted when magnesium sulfate is administered to patients in whom PTB is threatened	All costs are presented in 2011 Canadian dollars ($1CAN=$1US=£0.62) Both costs and QALYs were discounted at 3% annually for the base case analyses
Cahill et al.[16]	USA	To estimate the cost-effectiveness of magnesium sulfate neuroprophylaxis for all females at risk for PTB before 32wks from a societal perspective	Decision analytic and cost-effectiveness model	Life expectancy of 75y	Magnesium sulfate therapy for the prevention of CP in infants born preterm	No treatment	Females carrying singleton pregnancies between 24wks 0/7d and 31wks 6/7d gestation at high risk for spontaneous PTB 32wks' gestation due to either PTL or PPROM	Magnesium sulfate for neuroprophylaxis led to lower costs (USD$1739 vs USD$1917) and better outcomes (56.684 vs 56.678 QALYs) For every 10,000 females at risk for preterm birth treated with magnesium, USD$1.8 million were saved and 52 QALYs were gained	

Table II: Continued

References	Country	Aim	Study type	Time horizon	Population	Comparison	Population	Study results	Comments
Cahill et al.[15]	USA	To estimate the cost-effectiveness of magnesium neuroprophylaxis for all females at risk for PTB before 32wks from a societal perspective	Decision analytic and cost-effectiveness model		Magnesium sulfate therapy for the prevention of CP in infants born preterm	No treatment		Magnesium for neuroprophylaxis was the dominant strategy (i.e. less expensive and more effective) Considering an annual birth rate of 4 million births, a strategy for magnesium sulfate for neuroprophylaxis would prevent 904 cases of moderate-to-severe CP each year	
Vijgen et al.[17]	the Netherlands	To establish the cost-effectiveness of two strategies of fetal surveillance during labour to prevent CP	A trial-based economic evaluation from a health care provider perspective		Fetal surveillance during labour with cardiotocography plus ST analysis	Cardiotocography only		The ICER was €167,854 per prevented case of CP when using ST analysis vs cardiotocography only, and varies between €78,719 and €393,594 when using probabilities between 6% and 30% In the trial the number of cases with metabolic acidosis was 20 in the ST analysis group (n=2827) and 30 in the cardiotocography group (n=2840) Addition of ST analysis reduces the risk of CP at a considerable cost per case	Resources used were documented by specific items in the CRFs Unit costs for ST analysis were based on depreciation costs of the medical devices purchase prices, as well as training costs for obstetricians The probability of developing CP after metabolic acidosis was 14% as derived from a literature review

Table II: Continued

References	Country	Aim	Study type	Time horizon	Population	Comparison	Population	Study results	Comments
BoNT-A injection									
Tapias et al.[18]	Spain	To conduct a CMA of Abo-BoNT-A vs Ona-BoNT-A in treating patients with paediatric spasticity	CMA alongside a observational longitudinal study	Average time of follow-up: 18.6mo for Abo-BoNT-A and 19.06mo for Ona-BoNT-A	Abo-BoNT-A	Ona-BoNT-A	936 spastic children aged 2–18y treated in the paediatric neurology unit of a Spanish hospital	No significant difference in the treatment effectiveness between the two BoNT-A. Therefore, a CMA was conducted The mean pharmacological cost per patient and year was €480 for Ona-BoNT-A and €287 for Abo-BoNT-A, which represents annual savings in favour of Abo-BoNT-A of €193 in pharmacological cost The total annual direct cost obtained was €839 for Ona-BoNT-A and €631 for Abo-BoNT-A, representing a difference of €208 per year in favour of treatment with Abo-BoNT-A	The analysis was conducted from the perspective of the NHS, considering direct costs only: pharmacological costs (manufacturer's selling price) and costs of visits in 2016 Euros if the 'typical patient' profile is considered in sensitivity analysis, the potential pharmacological savings with Abo-BoNT-A would be €295 per patient per year
Catsman-Berrevoets et al.[19]	the Netherlands	To compare effectiveness and cost-effectiveness of BoNT-A+iPT vs only intensive PT treatment in a RCT	RCT		BoNT-A followed by iPT (n=41)	Intensive PT only (n=24)	65 children with CP aged 4–12y	No statistically significant evidence was found for added value of BoNT-A injections in BoTN-A+iPT treatment for the primary outcomes Average treatment costs (including plaster and Ankle-Foot-Orthosis) were significantly higher in BoNT-A+iPT than in iPT (€8.963 vs €6.182; p=0.001)	

Table II: Continued

References	Country	Aim	Study type	Time horizon	Population	Comparison	Population	Study results	Comments
Yagudina et al.[20]	Russia	To conduct a CEA of Abo-BoNT-A+standard therapy, Ona-BoNT-A+standard therapy and standard therapy solely in patients with spastic CP	Decision tree model		Abo-BoNT-A+standard therapy vs Ona-BoNT-A+standard therapy vs standard therapy solely	Standard therapy includes centrally acting muscle relaxant, physiotherapy, casting, and orthosis		The Abo-BoNT-A+standard therapy helps to avoid surgical intervention in 93% of patients vs 90% of patients with Ona-BoNT-A+standard therapy and for 48% of patients with standard therapy. The Abo-BoNT-A+standard therapy has the lowest cost-effectiveness ratio (RUB$11,509 /USD$215) in comparison with drug therapy Ona-BoNT-A+standard therapy (RUB $ 12,872/USD$238) and standard therapy with a centrally acting muscle relaxant without BoNT-A (RUB$27,715/USD$467) by the end of 2y of treatment	The data on drugs efficacy (measured as proportion of patients with spastic forms of CP, avoided orthopaedic surgery at second year of therapy) was obtained from available clinical trials. The following costs were taken into account: the costs of pharmacotherapy, inpatient and outpatient care, costs of adverse events, sanatorium–resort medical care, casting orthopaedic surgeons, disability pensions, disabled child care benefit
Houltram et al.[21]	Australia	To compare two methods of conservative management of calf spasticity and equinus gait ± intramuscular injection of BoNT-A and serial casting	A cost consequence analysis with a simple economic modelling approach to establish resource utilization by treatment arm		BoNT-A in the management of equinus in children with CP	Serial casting	Children with CP	The RCTs demonstrated equivalent efficacy of BoNT-A and serial casting; however, with BoNT the effect lasted longer and was clearly the preferred treatment For patients with hemiplegia the total additional cost, discounted at 5% annually, for BoNT-A is AUD$793 For patients with diplegia the total additional cost for BoNT-A is AUD$867	The economic evaluation was undertaken as part of an application to the PBAC to obtain reimbursement for BOTOX Only direct medical costs were considered (BoNT-A, medical personnel time and medical consumables) The costs associated with the treatment of adverse events have not been considered because the adverse effect is reversible

Table II: Continued

References	Country	Aim	Study type	Time horizon	Population	Comparison	Population	Study results	Comments
ITB therapy									
Bensmail et al.[22]	France	To assess the cost-effectiveness of ITB therapy	Modelling study	Various treatment sequences over 2y	ITB therapy	Compared with conventional medical treatments for disabling spasticity	Patients with disabling spasticity and functional dependence caused by any neurological disease	ITB therapy model revealed a lower cost (€59,391 vs €88,272; $p<0.001$) and an overall more favourable cost-effectiveness ratio (€75,204/success vs €148,822/success; $p<0.001$), compared with conventional medical management without ITB	Direct medical costs were measured in Euros (2006) and based on a French retrospective cost survey at Raymond Poincaré Hospital by Bensmail et al. [22]
Hoving et al.[23]	the Netherlands	To compare the costs and health effects of CITB with those of standard treatment only, from the health care perspective	Combined CEA/CUA alongside the Dutch national study on the efficacy and safety of CITB for intractable spasticity in children with CP		CITB in children with intractable spastic CP	Standard treatment only		Gaining one QALY cost, on average, €32,737 (€28,273, using the UK EQ-5D index) Additional mean annual costs of CITB €3732 and the mean intervention-related health care costs at €4226 per year	Health effects were expressed in terms of a VAS for individual problems and QALYs, derived from the Dutch EQ-5D index Included intervention costs and other health care costs. For the latter, data were collected by means of a questionnaire and a cost diary Costs were estimated for the year 2003 in Euros. We discounted costs that were not available for the year 2003 with 4% per year according to the Dutch guidelines
de Lissovoy et al.[24]	USA	To assess the cost-effectiveness of ITB among children with severe spasticity of cerebral origin	CUA using mathematical modelling and computer simulation		ITB therapy for the treatment of severe spasticity associated with CP	Alternative medical and surgical therapy	Children with severe spasticity of cerebral origin who have not responded to less invasive treatments such as oral medications; over a 5y episode of treatment	ITB therapy increased the 5y cost of treatment by $49,000 relative to alternative treatment accompanied by an average gain of 1.2 QALY The net result was an incremental cost-effectiveness ratio of USD $42,000 per QALY All costs were adjusted to base year 2003. Both costs and QALYs are discounted at an annual rate of 3%	HUI-2 to rate health states associated with the course of treatment by a panel of clinicians Data on treatment costs representative of these children were derived from a health insurance claims database that included both commercial and Medicaid data

Table II: Continued

References	Country	Aim	Study type	Time horizon	Population	Comparison	Population	Study results	Comments
Other treatment/intervention									
Comans et al.[27]	Australia	To estimate the cost-effectiveness of a training system for improvements in upper-limb function for children with unilateral CP	CEA alongside a randomized controlled trial	20wks	The 'Move it to improve it' (Mitii) therapy is a web-based system designed to facilitate intensive motor planning, upper limb, gross motor, and cognitive rehabilitation	Usual care	102 children aged 8–18y with unilateral spastic CP (GMFCS level I or II)	The intervention group had significantly higher proportions of responders in two subscales of the AMPS and the two subscales of the COPM. Power to detect a significant difference was at least 88% for all four outcomes (AMPS-M, AMPS-P, COPM-P, COPM-S responder) ICER ranged from AU$3078 to $4191 per one unit of effectiveness measured by AMPS or COPM. Bootstrapped credible intervals ranged from AUD$1553 for AMPS-P to AUD$9574 for COPM-P.	
Slaman et al.[28]	the Netherlands	To evaluate the cost utility of a lifestyle intervention among adolescents and young adults with CP	CUA alongside a single-blind, RCT		6mo lifestyle intervention consisting of physical fitness training combined with counselling sessions focusing on physical behaviour and sports participation	Usual care, no intervention to improve physical behaviour and fitness	57 adolescents and young adults with spastic CP	No significant differences between groups were found for direct medical costs or productivity costs A cost-utility ratio of –€23,664 per QALY was found for the lifestyle intervention vs no treatment	QALYs were derived from the SF-36 questionnaire using the SF-6D

QALY, quality-adjusted life-year; PTB, preterm birth; PTL, preterm labour; PPROM, preterm premature rupture of membranes; ICER, incremental cost-effectiveness ratio; CRF, case report form; BoNT-A, botulinum toxin A; CMA, cost-minimization analysis; NHS, National Health Service; PT, physiotherapy; RCT, randomized controlled trial; iPT, intensive physiotherapy; CEA, cost-effectiveness analysis; PBAC, Pharmaceutical Benefits Advisory Committee; ITB, intrathecal baclofen; CUA, cost-utility analysis; CITB, continuous ITB; EQ-5D, EuroQol-5D; VAS, visual analogue scale; HUI, Health Utilities Index; GMFCS, Gross Motor Function Classification System; AMPS, Assessment of Motor and Process Skills; COPM, Canadian Occupational Performance Measure; SF-36; Short Form-36; SF-6D, Short Form-6D; ST, segment waveform analysis of the fetal electrocardiogram.

Further, a more recent RCT (2015) showed no statistically significant evidence for the added value of BoNT-A treatment followed by intensive physiotherapy compared with intensive physiotherapy alone.[19] The trial found trends towards the intervention effect in favour of only intensive physiotherapy for improving gross motor function (p=0.095), decreasing sedentary behaviour during everyday physical activity (p=0.087), and improving quality of life (p=0.066). The addition of BoNT-A to physiotherapy improved everyday physical activity over 24 weeks' follow-up (p=0.064), with a significantly higher treatment cost (€8963 vs €6182; p=0.001). The higher treatment cost did not seem to be warranted for the improved daily physical activity in the short-term, but long-term impact is uncertain.

A third modelling study constructed a decision-tree model to simulate the effects of Abo-BoNT-A, Ona-BoNT-A, and standard therapy.[20] Treatment efficacy, measured as the proportion of patients with spastic CP who avoided orthopaedic surgery at the end of 2 years of therapy, was obtained from available clinical trials. Abo-BoNT-A plus standard therapy is the most cost-effective treatment choice with the lowest ICER. Similar results were found in another, more recent economic study of BoNT-A treatment in which two types of BoNT-A (i.e. Abo-BoNT-A and Ona-BoNT-A) were compared in 895 paediatric patients aged 2 to 18 years with spasticity.[18] This was a cost-minimization analysis, where the treatment effectiveness was equivalent between the two drugs, conducted alongside a longitudinal observational study. The total direct cost (pharmacological and medical visits) difference was €208 per year per child in favour of treatment with Abo-BoNT-A.

ITB

Despite the limited efficacy base, there were three economic evaluation studies on ITB, two modelling studies and one cost-effectiveness analysis (CEA)/cost-utility analysis (CUA) alongside a national study on the efficacy of ITB.[22–24] The modelling studies aimed to simulate real-life scenarios.

One modelling study compared the cost-effectiveness of ITB used as the first-line treatment with all other conventional treatment options offered to patients with spasticity.[22] The comparator was a package of specific current treatments based on the most established French treatment patterns, namely physical therapy only, oral antispasticity agents, focal spasticity treatments, neurosurgical interventions, nursing care, and ITB (plus ITB potential adjustment dose plus potential pump removal). Two decision trees were constructed by simulation models using computer programming languages that aimed to replicate real-life clinical practices. Using ITB as the first-line strategy in severely impaired individuals with disabling spasticity had a significantly higher success rate than conventional medical management (78.7% vs 59.3%; p<0.001). ITB was considered to be the dominant strategy providing greater effectiveness at a lower cost.

In a further study, an ICER of USD$42 000 per QALY in a CUA was reported.[24] The likelihood that ITB has a cost per QALY of less than or equal to USD$50 000 was greater than 70%. Similar to the modelling study discussed above,[22] the CUA compared ITB with a conventional medical approach among children who had not responded to less-invasive treatments such as oral medications. A mathematical model simulated the experience of two groups of children, an ITB group and an alternative treatment group, followed over a 5-year treatment period. Based on results of 15 studies selected by the authors to identify the typical symptom profile of a child with severe spasticity, five health states were established to describe a typical child receiving ITB. Utility weights for each health state were rated by a panel of nine clinicians using the Health Utilities Index.[35] By drawing random samples with bootstrapping techniques from the appropriate sets of utility and cost values, the model created a set of data points for members of each of the two cohorts. ICERs were derived from the bootstrapping data sets of cost and utility that generated QALY over a 5-year period.

In contrast to these desk-top modelling studies, a CEA/CUA was carried out alongside a Dutch national study on the efficacy and safety of ITB therapy for children with CP.[23] Data were collected from a sample of 15 young people aged between 7 years and 17 years at the time of pump implantation with Gross Motor Function Classification System levels III to V. The economic evaluations compared the costs and health effects of ITB with standard treatment only, for a 1-year period. Standard treatment included physical therapy, occupational therapy, and/or rehabilitation. Both the CEA and the CUA was undertaken from the health care perspective, taking into account all relevant resources consumed. Additional health effects of ITB were assessed by using the visual analogue scale for individual problems in the CEA and the EuroQol-5D in the CUA.[36] Owing to the small sample size, bootstrapping methods were undertaken to verify the reliability of the results with 1000 replications. The results showed ITB therapy was cost-effective by improving health outcome at a reasonable cost with an ICER of €32 737 per QALY (using the Dutch EuroQol-5D index) and €28 273 per QALY (using the UK EuroQol-5D index).

Other therapies and interventions for treating CP

Recently, a CEA was conducted alongside an RCT to estimate the cost and benefits of providing a multimodal web-based program delivered at home to facilitate intensive motor planning, upper limb, gross motor, and cognitive rehabilitation.[27] The participants of the RCT were 102 children with spastic unilateral CP aged 8 to 18 years with Gross Motor Function Classification System level I or II and Manual Ability Classification Scale levels I and III. The ICER results reported as 'cost per proportion of responders', defined as the minimum clinically important difference by either 0.3 logits on the Assessment of Motor or Process Skills or 2 points on the Canadian Occupational

Performance Measure, ranged from AUD$3078 to AUD $4191 compared with usual care. With modest costs and a significant difference in proportion of responders for the intervention group, the authors concluded that the intervention offered a cost-effective program adjunct to direct rehabilitation for limited costs and greater gains in health outcomes.

A CUA of a lifestyle intervention was evaluated alongside an RCT for 57 adolescents and young adults with CP aged 16 to 24 years.[28] The analysis examined a 6-month lifestyle intervention consisting of physical fitness training combined with counselling sessions (focused on physical behaviour and sports participation), compared with the control group who continued with usual care. Intervention costs, direct medical costs, and productivity costs were assessed, with 2009 Dutch reference unit prices. Quality of life was measured using the Short Form-36 and converted into Short-Form-6D utility scores.[37] The preliminary results showed the intervention group gained 0.0131 QALYs with a lower annual total cost of €310, compared with the control group. However, none of the comparisons in cost or outcome between the two groups were statistically significant. Bootstrapping results showed 86% of ICERs were less €20 000 per QALY. The study suggests a lifestyle intervention is cost-saving or cost-effective compared with offering no intervention to improve movement behaviour and fitness among young people with CP.

Costing studies of treatment for CP

BoNT-A injection

Two budget impact analyses, undertaken in the UK and the Russian Federation, showed that Abo-BoNT-A was a less costly treatment than other BoNT-A injections, for example Ona-BoNT-A or Inco-BoNT-A.[38,39] In the UK study, treatment with BoNT-A for patients with upper-limb spasticity was less costly than 'best supportive care' per patient per year. Note that the meaning of 'best supportive care' varies from country to country. In this study an increased uptake of Abo-BoNT-A resulted in a 5-year saving of £6 283 829 from the UK payer's perspective.

A retrospective clinical notes review in Germany on children treated with BoNT-A showed an 85% reduction in the percentage of children requiring surgery and 60% shorter average length of stay than the control group who would be eligible but did not receive the treatment.[40] The total cost of managing a patient receiving BoNT-A during their first year of treatment was found to be €16 700. The comparable cost of managing a control group patient was €33 800. The researchers concluded that the use of BoNT-A released resources for alternative use during the first year after treatment, without any loss of clinical improvement.

ITB therapy

A retrospective database analysis using actuarial methods was carried out to investigate the cost associated with ITB therapy for adjunct spasticity control versus continued conventional medical management in the absence of ITB therapy (ITB-free).[41] Cost projections were developed over a 30-year time horizon. Costs in the month of implant and in the following year were USD$26 375 more than conventional management. However, financial break-even occurred between the second and third years postITB implant. The lifetime analysis indicated that ITB was cost saving, with USD$8009 saved per patient per year compared with conventional therapy (3% discount rate; 2007 reference year). Most of the savings were derived from reductions in inpatient admissions, physician office visits, and outpatient physiotherapy. However, another study that compared 9 months before and after implantation of ITB indicated no significant difference in total costs.[42]

Surgical procedures

A micro-costing study detailing cost components associated with an intervention, was conducted to determine health care costs of upper-extremity surgical correction in 39 children with spastic CP at a Dutch hospital.[43] The average hospital cost was €6813 per child (reference year 2014), consisting of medical costs from the first contact until 9 months after surgery. Rehabilitation costs were estimated at €3599 per child with an average of 3.5 months duration of the rehabilitation program.

A costing exercise to produce patient level costing data for all instrumented scoliosis corrections was performed to inform a national tariff for paediatric spinal surgery in the UK.[44] A total cost of £20 340 was estimated from 23 patients with non-idiopathic scoliosis with neuromuscular, CP, congenital, and syndromic scoliosis. Another retrospective review of 74 surgical patients with neuromuscular scoliosis (28% with CP) indicated a total (SD) surgical cost of USD$50 096 (USD$23 998).[45] Major contributors to the cost of scoliosis surgery were implants, inpatient and intensive care unit costs, and bone grafts.

Gait analysis

One study concluded that computerized gait analysis was a potentially useful technology in the management of children with walking disabilities, but its efficacy had not been established.[46] Later, a retrospective study in 462 ambulatory patients with CP was conducted to compare the number of procedures and total costs between groups of patients undergoing gait analysis versus no gait analysis.[47] Adjusting for age, CP type, ambulatory status, Gross Motor Function Classification System level, and follow-up time, patients in the gait analysis group had more procedures (gait analysis: 5.8; no gait analysis: 4.2; $p<0.001$) and higher costs (gait analysis: CAN $43 006; no gait analysis: CAN$35 215; $p<0.001$) during index surgery but less subsequent surgery after the index surgery. Patients in the NGA group were twice as likely to have undergone additional surgery than patients in the gait analysis group (adjusted hazard ratio 2.1; $p=0.002$).

DISCUSSION

When interpreting the findings of this review, it is important to note that the term 'economic evaluation' has a very

specific meaning and flows from the overarching economic principle of 'opportunity cost' – that in choosing one action we give up the benefits that might flow from alternative actions. This underlies the concept of efficiency – that of maximizing net benefit (i.e. benefit gained vs benefit forgone) with resource use, which is the mechanism that enables measurement of benefits gained or forgone. In applying this principle, economic evaluation must involve a comparison of alternatives (often 'current practice' vs an 'option for change') and must involve an analysis of both costs and benefits. A comparison of only outcomes may establish efficacy/effectiveness, a comparison of only costs may establish the cheapest option; however, both are required for cost-effectiveness. Similarly, a comparison of cost and outcomes for a single intervention is a cost-outcome description; it is not an economic evaluation. Economic evaluation can be conducted either alongside clinical studies, such as RCTs, or by a modelling approach that constructs mathematical relationships to simulate relevant consequences, such as disease progression, using the best available information. The modelling study is helpful in the absence of data certainty or when real-life studies are too difficult to conduct.

The generic concept of efficiency is further refined to target one or both of two key questions: (1) should an intervention be undertaken or ceased (i.e. value-for-money or 'allocative efficiency'); and (2) if an intervention is to be undertaken, how should it be designed (i.e. 'technical efficiency'). There are different types of economic evaluations to answer these questions, mainly differentiated on the basis of how they measure benefit. Evaluations that focus on the measurement of clinical and/or physical outcomes are called CEAs and are often closely linked to the primary and secondary outcomes of trials. Evaluations that focus on measurement of quality of life are called CUAs and require preference-based utility instruments. Evaluations that focus on measuring benefit in dollar terms are called cost–benefit analyses. The different types of economic evaluation have different credentials in terms of whether they can address allocative and/or technical efficiency. The most preferred intervention is, in economic terms, a dominant intervention, which both saves cost and improves health outcomes. Following the notion of 'dominant', a cost-effective intervention is one that improves health at additional cost with a lower ICER value. However, there is no explicit ICER threshold established; instead, a general rule of thumb, for example less than $50 000 per QALY is commonly used in countries like Australia, the UK, and Canada.[48]

It is challenging to compare cost and cost-effectiveness of different treatment and interventions in a direct way, as the decision contexts and the health care systems are diverse. More importantly, the treatment and interventions for CP all have different indications so that clinicians and policy-makers should not make decisions merely based on the economic considerations. Clinical judgement and economic value judgement should be critically examined side by side. Judging the economic credential using common outcome measures, such as cost per QALY in CUA, is preferable to using different outcomes in cost-effectiveness measured by different studies. A number of studies in this review reported incomparable ICERs, so that a value judgement could not be formed. For example, cost per proportion of responders by the specific measurements in the multimodal web-based program RCT are of limited use as they cannot be compared to other interventions without this specific outcome measurement.[27] Caution is always required when comparing one study to another as assumptions are sometimes made, particularly in modelling studies in which assumptions made for the model parameters could impact on the conclusions.

The studies reported provide evidence that prevention of CP using magnesium sulfate in preterm births is cost-effective.[14–16] Substantial lifetime costs attributable to CP have been reported in the USA and Europe, with the latest estimate up to USD$921 000 per person.[49–51] In Australia, the annual cost per person with CP was estimated at AUD $43 431 and at AUD$115 000 if the disability and premature death was included.[52] In Australia, the number of pre- and perinatally acquired CP cases over the 1993 to 2006 period was estimated to be 4817.[6] If effective prevention of pre- and perinatally acquired CP can be achieved, the reduction in CP cases in Australia could be translated into direct and indirect financial costs of AUD$67million per year averted by applying the Australian annual cost per person with CP.[52] Put another way, the reduction in CP cases equates to a lifetime cost of USD$4.4billion averted, if the US estimate of lifetime costs is applied.[50] Current economic modelling studies on the use of magnesium sulfate suggest the intervention is a 'dominant strategy' for imminent preterm birth.[16] With this 'back of the envelope' calculation, it can readily be seen that effective prevention strategies like magnesium sulfate could bring substantial relief to the health care system, to the welfare system, to individuals and their families, and to government.

Administration of magnesium sulfate in females at risk of preterm birth is the most promising intervention to prevent CP in terms of cost-effectiveness to date among the 15 included economic evaluation publications. The intervention of magnesium sulfate for fetal neuroprotection is either dominant or very cost-effective, depending on the risk level of preterm birth and the perspective taken by the analysis. Strong evidence of the benefit of magnesium sulfate in preventing CP among infants born very preterm has led to the development of guidelines for its use which have been endorsed by the Australasian College of Obstetricians and Gynaecologists and the National Health and Medical Research Council.[53] However, the uptake of these guidelines has been limited and magnesium sulfate is only used as a strategy to prevent CP in a small number of females. Nevertheless, 57% of CP cases occur in infants born at term where magnesium sulfate has no role in preventing CP.[5]

In contrast, the fetal surveillance during labour intervention was not cost-effective, with ICERs that varied between

€78 719 and €393 594 per CP case prevented. In the majority of CP cases, the underlying injury occurred before labour onset. There is evidence of peripartum asphyxia in only about 10% of term births resulting in CP. Accordingly, no matter how effective intrapartum fetal surveillance is in detecting fetal hypoxia/asphyxia, it will only afford opportunities for mitigation in a small number of cases. The ICER results are limited in assessing the technical efficiency to determine what is the best way to undertake fetal surveillance, with what modality, and in which target population. New research areas in the prevention of CP in high-risk populations include use of antioxidant therapies (e.g. melatonin) in the perinatal period to protect the fetus, particularly the developing brain, against oxidative stress in pregnancy and at birth.[54] Further evidence of efficacy and effectiveness is required.

In addition to prevention of CP, the economic analysis of CP included studies of BoNT-A and ITB. Modelling simulation studies suggest that ITB could be cost-effective or cost-saving, although its efficacy is still to be verified by stronger evidence.[22–24] However, inconsistent results of the cost-effectiveness for BoNT-A injection have been reported from four economic evaluation studies, mainly owing to the additional effectiveness of the treatment compared with the chosen comparator, for example serial casting, intensive physiotherapy, or standard treatment.[19–21] Furthermore, some results are indicative and do not constitute strong evidence of value-for-money without evaluating long-term effect or reporting ICER by QALYs. BoNT-A injection is better for purely dynamic equinus but often it is used for mixed equinus when there is some contracture. Serial casting might by slightly superior to BoNT-A injection when there is a little more contracture.[33,55] This raises the importance of critical considerations in the clinical context. In contrast, for economic considerations, without a unified comparator it is difficult to draw conclusions about the economic value of the treatment. Nevertheless, it is clear from studies comparing different types of BoNT-A that Abo-BoNT-A is the most economical choice compared with other types with equivalent treatment effect.

There is evidence in the literature that BoNT-A injection is effective for CP management (e.g. spasticity, motor function), but the results are inconsistent. BoNT-A injection for the upper limbs has been used with good efficacy if combined with therapy to reduce spasticity and improve hand function;[56,57] other studies have shown that BoNT-A injection is ineffective for hip displacement.[58,59] One animal study suggests that repeat BoNT-A injections may have potential harm in dramatically reducing muscle torque and producing fibrosis.[60] BoNT-A injection is considered effective for the following goals: reduction of upper- and lower-limb spasticity; improved walking abilities; improved hand function and performance of functional hand activities in combination with occupational therapy; and reduction in drooling.[61] BoNT-A has been used in young children to reduce spasticity in multiple muscles before children are old enough to undergo surgical procedures. There is a debate, however, about its overall clinical benefits. Two RCTs investigating BoNT-A injection frequency concluded that yearly injection versus every 4 months achieved the same treatment outcomes for lower-limb spasticity in children with CP.[62,63] Substantial savings, in medical costs and cost to the families in time and travel, would be made if the BoNT-A regimen was reduced from every 4 months to yearly injections. Based on the current economic evaluation assessment, use of BoNT-A injection may be cost-effective, but further research is needed on its overall cost-effectiveness for different applications in CP management.

Many budget impact analyses and costing studies assessed the cost of BoNT-A versus control groups. The selection of comparator ranged from 'best supportive care' to 'usual care'. The meaning of 'best supportive care' or 'usual care' will vary from country to country and also within countries. Therefore, it is hard to draw conclusions as to whether cost savings in using BoNT-A to manage CP in one country are applicable to another country.

The current economic evaluation literature regarding ITB therapy suggests that the intervention is cost-effective in the short term and could be a dominant strategy in the long term. However, the efficacy and effectiveness of the therapy has not been well established and stronger evidence is required. According to a 'systematic review of systematic reviews on best available intervention evidence for children with CP', ITB therapy was graded as a 'yellow' intervention, that is, where predominantly low-quality supporting evidence is available and the size of the gains varied between studies.[61] It was graded as a 'probably do it' intervention, but quality and well-designed clinical trials are necessary to verify efficacy. ITB may benefit children with severe spasticity of cerebral origin who have not responded to less invasive treatments such as oral medications.

Cost-effectiveness ratios were presented by some studies that were not economic evaluations, that is, by cost outcome descriptions. This can create confusion for readers and such studies need to come with a warning that the information provided is descriptive and does not report efficiency. Economic evaluations should report incremental costs in relation to incremental outcomes. However, ICERs were not often reported. There are various guidelines for critical appraisal/reporting of economic evaluation studies; but no universally accepted criterion standard is used.[12,64,65]

CONCLUSION

It is clear from the present systematic review that the economics of CP is under-researched and more economic studies in this topic, as well as long-term clinical studies, are needed to provide robust evidence to inform value judgements. At this time, successful prevention in CP would clearly avoid significant costs. The administration of magnesium sulfate for imminent preterm birth is a dominant strategy resulting in less cost and more benefit

compared with no treatment. However, guidelines for the use of magnesium sulfate in preterm labour are not well adhered to and it will not benefit the large proportion of infants born at term.

Economic evaluation of ITB therapy suggests that the intervention is cost-effective, but stronger evidence for long-term effects is needed. Implantation of the ITB drug delivery system is expensive and makes no difference in the short term; however, ITB may be a cost-saving intervention in the long term. BoNT-A injection is more costly than other conventional therapies (e.g. serial casting and physiotherapy), but the evidence for additional treatment benefits is inconclusive and the long-term effects are uncertain.

A web-based home therapy program is considered very cost-effective with improvements in motor skills and occupational performance. A lifestyle intervention could be cost-saving or cost-effective compared with offering no intervention to improve movement behaviour and fitness. Gait analysis is a potentially useful technology.

There are large gaps in the evidence that is available about the effectiveness of interventions, as well as a lack of high-quality economic appraisal in clinical studies. Continuing to build evidence about both the clinical and economic outcomes of interventions aiming to prevent CP or to improve outcomes for individuals with CP is critical for policy-making and service delivery.

ACKNOWLEDGEMENTS

We are grateful for the comments and feedback on our work from the members of the project consultation group: Professor Dinah Reddihough, Murdoch Children's Research Institute, Melbourne; Professor H Kerr Graham, Royal Children's Hospital, Melbourne; Professor Christine Imms, Australian Catholic University; Professor Nadia Badawi, Cerebral Palsy Alliance; Dr Elise Davis, University of Melbourne; Professor Eve Blair, University of Western Australia; Professor Iona Novak, Cerebral Palsy Alliance; Dr Sarah McIntyre, Cerebral Palsy Alliance; Dr Helen Bourke-Taylor, Monash University; Professor Euan Wallace, Monash University; Professor Michael Fahey, Monash University. We thank the Victorian Managed Insurance Authority and Centre of Research Excellence in Cerebral Palsy for funding support for this systematic review. Any opinions, findings and conclusions, or recommendations expressed in this paper are those of the authors and do not necessarily reflect the views of the Victorian Managed Insurance Authority. The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

REFERENCES

1. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007; **109**: 8–14.
2. Graham HK, Rosenbaum P, Paneth N, et al. Cerebral palsy. *Nat Rev Dis Primers* 2016; **2**: 15083.
3. Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalance of cerebral palsy: a systematic review and meta-analysis. *Dev Med Child Neurol* 2013; **55**: 509–19.
4. Gladstone M. A review of the incidence and prevalance, types and aetiology of childhood cerebral palsy in resource-poor settings. *Ann Trop Paediatr* 2010; **30**: 181–96.
5. Australian Cerebral Palsy Register Group. Australian Cerebral Palsy Register Report 2016. Sydney, NSW: Australia, 2016.
6. Australian Cerebral Palsy Register Group. Australia and the Australian Cerebral Palsy Register for the birth cohort 1993 to 2006. *Dev Med Child Neurol* 2016; **58** (Suppl. 2): 3–4.
7. Reid SM, Meehan E, McIntyre S, Goldsmith S, Badawi N, Reddihough DS. Temporal trends in cerebral palsy by impairment severity and birth gestation. *Dev Med Child Neurol* 2016; **58**(Suppl. 2): 25–35.
8. Bourke-Taylor H, Howie L, Law M, Pallant JF. Self-reported mental health of mothers with a school-aged child with a disability in Victoria: a mixed method study. *J Paediatr Child Health* 2012; **48**: 153–9.
9. Eker L, Tüzün EH. An evaluation of quality of life of mothers of children with cerebral palsy. *Disabil Rehabil* 2004; **26**: 1354–9.
10. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. [Internet] 2011. Available from: http://handbook.cochrane.org (accessed 15 October 2015).
11. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e10000097.
12. Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. Methods for the Economic Evaluation of Health Care Programmes. Oxford, UK: Oxford University Press UL, 2015.
13. Tonmukayakul U, Shih S, Carter R. Literature Review & Synthesis for VMIA – Cerebral Palsy: Interventions & Health Economics. Geelong, Vic.: Deakin University, 2016.
14. Bickford CD, Magee LA, Mitton C, et al. Magnesium sulphate for fetal neuroprotection: a cost-effectiveness analysis. *BMC Health Serv Res* 2013; **13**: 527.
15. Cahill A, Odibo A, Stout M, Grobman W, Macones G, Caughey A. Is magnesium sulfate therapy for the prevention of cerebral palsy in preterm infants cost-effective? *Am J Obstet Gynecol* 2009; **201**: S83.
16. Cahill AG, Odibo AO, Stout MJ, Grobman WA, Macones GA, Caughey AB. Magnesium sulfate therapy for the prevention of cerebral palsy in preterm infants: a decision-analytic and economic analysis. *Am J Obstet Gynecol* 2011; **205**: 542.e1–7.
17. Vijgen SM, Westerhuis ME, Opmeer BC, et al. Cost-effectiveness of cardiotocography plus ST analysis of the fetal electrocardiogram compared with cardiotocography only. *Acta Obstet Gynecol Scand* 2011; **90**: 772–8.
18. Tapias G, García-Romero M, Crespo C, Cuesta M, Forné C, Pascual-Pascual SI. Cost-minimization analysis in the treatment of spasticity in children with cerebral palsy with botulinum toxin type A: an observational, longitudinal, retrospective study. *Farm Hosp* 2016; **40**: 412–26.
19. Catsman-Berrevoets CE, Bussmann JBJ, Pangalila RF, et al. Treatment with botulinum toxin of children with cerebral palsy has no added therapeutical value or cost-effectiveness for gross motor function, everyday physical activity levels or quality of life when combined with intensive functional physiotherapy. *Eur J Paediatr Neurol* 2015; **19**: S11.
20. Yagudina R, Kulikov A, Ugrekhelidze D. Cost-effectiveness analysis of botulinum toxin type A treatment for cerebral palsy. *Value Health* 2015; **18**: A734.
21. Houltram J, Noble I, Boyd RN, Corry I, Flett P, Graham HK. Botulinum toxin type A in the management of equinus in children with cerebral palsy: an evidence-based economic evaluation. *Eur J Neurol* 2001; **8**(Suppl. 5): 194–202.
22. Bensmail D, Ward AB, Wissel J, et al. Cost-effectivenss modeling of intrathecal baclofen therapy versus other interventions for disabling spasticity. *Neurorehabil Neural Repair* 2009; **23**: 546–52.
23. Hoving MA, Evers SM, Ament AJ, van RE, Vles JS, Dutch Study Group on Child Spasticity. Intrathecal baclofen therapy in children with intractable spastic cerebral palsy: a cost-effectiveness analysis. *Dev Med Child Neurol* 2008; **50**: 450–5.
24. de Lissovoy G, Matza LS, Green H, Werner M, Edgar T. Cost-effectiveness of intrathecal baclofen therapy for the treatment of severe spasticity associated with cerebral palsy. *J Child Neurol* 2007; **22**: 49–59.

25. Taylor P, Humphreys L, Swain I. The long-term cost-effectiveness of the use of Functional Electrical Stimulation for the correction of dropped foot due to upper motor neuron lesion. *J Rehabil Med* 2013; **45**: 154–60.

26. Truong WH, Novacheck T, Shin E, et al. Should routine proximal femoral hardware removal be performed in children with cerebral palsy? *Dev Med Child Neurol* 2013; **55**(Suppl. 3): 13.

27. Comans T, Mihala G, Sakzewski L, Boyd RN, Scuffham P. The cost-effectiveness of a web-based multimodal therapy for unilateral cerebral palsy: the Mitii randomized controlled trial. *Dev Med Child Neurol* 2017; **59**: 756–61.

28. Slaman J, van den Berg-Emons R, Tan SS, et al. Cost-utility of a lifestyle intervention in adolescents and young adults with spastic cerebral palsy. *J Rehabil Med* 2015; **47**: 338–45.

29. Marret S, Marpeau L, Zupan-Simunek V, et al. Magnesium sulphate given before very-preterm birth to protect infant brain: the ranomised controlled PREMAG trial. *BJOG* 2007; **114**: 310–18.

30. Mittendorf R, Dambrosia J, Pryde PG, et al. Association between the use of antenatal magnesium sulfate in preterm labor and adverse health outcomes in infants. *Am J Obstet Gynecol* 2002; **186**: 1111–18.

31. Crowther CA, Hiller JE, Doyle LW, Haslam RR, Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. Effect of magnesium sulphate given for neuroprotection before birth: a randomized controlled trial. *JAMA* 2003; **290**: 2669–76.

32. Rouse DJ, Hirtz DG, Thom E, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med* 2008; **359**: 895–905.

33. Corry IS, Cosgrove AP, Duffy CM, McNeill S, Taylor TC, Graham HK. Botulinum toxin A compared with stretching casts in the treatment of spastic equinus: a randomised prospective trial. *J Pediatr Orthop* 1998; **18**: 304–11.

34. Flett PJ, Stern LM, Waddy H, Connell TM, Seeger JD, Gibson SK. Botulinum toxin A versus fixed cast stretching for dynamic calf tightness in cerebral palsy. *J Paediatr Child Health* 1999; **35**: 71–7.

35. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI): concepts, measurement properties and applications. *Health Qual Life Outcomes* 2003; **1**: 54.

36. Lamers LM, Stalmeier PFM, McDonnell J, Krabbe PFM, van Busschbach JJ. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. *Ned Tijdschr Geneeskd* 2005; **149**: 1574–8.

37. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002; **21**: 271–92.

38. Abogunrin S, Hortobagyi L, Remak E, Dinet J, Gabriel S, Bakheit AM. Budget impace analysis of botulinum toxin A therapy for upper limb spasticity in the United Kingdom. *Clinicoecon Outcomes Res* 2015; **7**: 185–93.

39. Yagudina R, Kulikov A, Ugrekhelidze D. Budget impace analsysis of botulinum toxin type A treatment for cerebral palsy in the Russian Federation. *Value Health* 2015; **18**: A752.

40. Ruiz FJ, Guest JF, Lehmann A, et al. Costs and consequences of botulinum toxin type A use. Management of children with cerebral palsy in Germany. *Eur J Health Econ* 2004; **5**: 227–35.

41. Saulino M, Guillemette S, Leier J, Hinnenthal J. Medical cost impact of intrathecal baclofen therapy for severe plasticity. *Neuromodulation* 2015; **18**: 141–9.

42. Morton RE, Gray N, Vloeberghs M. A controlled study of intrathecal baclofen in non-ambulant children with cerebral palsy. *Dev Med Child Neurol* 2010; **52**(Suppl. 4): 56–7.

43. Alewijnse JV, van Rooijen EM, Kreulen M, Smeulders MJC, Tan SS. A microcosting study of the surgical correction of upper extremity deformity in children with spastic cerebral palsy. *Dev Neurorehabil* 2017; **20**: 173–8.

44. Cole AA, Blythe ES, Breakwell LM, Michael ALR. Patient level costing for instrumented paediatric scoliosis correction. *Eur Spine J* 2014; **23**: S133–4.

45. Diefenbach C, Ialenti MN, Lonner BS, Kamerlink JR, Verma K, Errico TJ. Hospital cost analysis of neuromuscular scoliosis surgery. *Bull Hosp Jt Dis (2013)* 2013; **71**: 272–7.

46. Hailey D, Tomie J. An assessment of gait analysis in the rehabilitation of children with walking difficulties. *Disabil Rehabil* 2000; **22**: 275–80.

47. Wren TA, Kalisvaart MM, Ghatan CE, et al. Effects of preoperative gait analysis on costs and amount of surgery. *J Pediatr Orthop* 2009; **29**: 558–63.

48. Henry DA, Hill SR, Harris A. Drug prices and value for money: the Australian Pharmaceutical Benefits Scheme. *JAMA* 2005; **294**: 2630–2.

49. Centers for Disease Control and Prevention (CDC). Economic costs of birth defects and cerebral palsy – United States, 1992. *MMWR Morb Mortal Wkly Rep* 1995; **44**: 694–9.

50. Centers for Disease Control and Prevention (CDC). Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment – United States, 2003. *MMWR Morb Mortal Wkly Rep* 2004; **53**: 57–9.

51. Kruse M, Michelsen SI, Flachs EM, Brønnum-Hansen H, Madsen M, Uldall P. Lifetime costs of cerebral palsy. *Dev Med Child Neurol* 2009; **51**: 622–8.

52. Access Economics. The Economic Impact of Cerebral Palsy in Australia in 2007. Sydney, NSW: Access Economics Pty Limited for Cerebral Palsy Australia, 2008.

53. Badawi N. Cerebral palsy – at last it's time to talk about prevention and maybe even cure. *Dev Med Child Neurol* 2012; **54**(Suppl. 5): 5.

54. Miller SL, Wallace EM, Walker DW. Antioxidant therapies: a potential role in perinatal medicine. *Neuroendocrinology* 2012; **96**: 13–23.

55. Hayek S, Gershon A, Wientroub S, Yizhar Z. The effect of injections of botulinum toxin type A combined with casting on the equinus gait of children with cerebral palsy. *J Bone Joint Surg* 2010; **92**: 1152–9.

56. Olesch CA, Greaves S, Imms C, Reid SM, Graham HK. Repeat botulinum toxin-A injections in the upper limb of children with hemiplegia: a randomized controlled trial. *Dev Med Child Neurol* 2010; **52**: 79–86.

57. Hoare BJ, Wallen MA, Imms C, Villanueva E, Rawicki HB, Carey L. Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (UPDATE). *Cochrane Database Syst Rev* 2010; CD003469.

58. Graham HK, Boyd R, Carlin JB, et al. Does botulinum toxin a combined with bracing prevent hip displacement in children with cerebral palsy and "hips at risk"? A randomized, controlled trial. *J Bone Joint Surg Am* 2008; **90**: 23–33.

59. Willoughby K, Ang SG, Thomason P, Graham HK. The impact of botulinum toxin A and abduction bracing on long-term hip development in children with cerebral palsy. *Dev Med Child Neurol* 2012; **54**: 743–7.

60. Minamoto VB, Suzuki KP, Bremner SN, Lieber RL, Ward SR. Dramatic changes in muscle contractile and structural properties after 2 botulinum toxin injections. *Muscle Nerve* 2015; **52**: 649–57.

61. Novak I, Mcintyre S, Morgan C, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013; **55**: 885–910.

62. Hastings-Ison T, Blackburn C, Rawicki B, et al. Injection frequency of botulinum toxin A for spastic equinus: a randomized clinical trial. *Dev Med Child Neurol* 2016; **58**: 750–7.

63. Kanovský P, Bares M, Severa S, Richardson A, Dysport Paediatric Limb Spasticity Study Group. Long-term efficacy and tolerability of 4-monthly versus yearly botulinum toxin type A treatment for lower-limb spasticity in children with cerebral palsy. *Dev Med Child Neurol* 2009; **51**: 436–45.

64. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996; **313**: 275–83.

65. Gold M, Siegel J, Russell L, Weinstein M. Cost-Effectiveness in Health and Medicine. Oxford, UK: Oxford University Press, 1996.