BMJ Open

Protocol for a systematic review of instruments for the assessment of quality of life and well-being in children and adolescents with cerebral palsy

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-015924
Article Type:	Protocol
Date Submitted by the Author:	10-Jan-2017
Complete List of Authors:	Mpundu-Kaambwa, Christine; University of South Australia, Business School Huynh , Elisabeth; University of South Australia, Business School Chen, Gang; Monash University, Centre for Health Economics Russo, Remo; Women's and Children's Hospital Adelaide, Paediatric Rehabilitation Ratcliffe, Julie; University of South Australia, Institute for Choice, Unisa Business School
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Paediatrics, Neurology, Qualitative research
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Developmental neurology & neurodisability < PAEDIATRICS, REHABILITATION MEDICINE

Protocol for a systematic review of instruments for the assessment of quality of life and well-being in children and adolescents with cerebral palsy

Authors: Christine Mpundu-Kaambwa[1*], Elisabeth Huynh[1] Gang Chen[2], Remo Russo[3,4], Julie Ratcliffe[1]

[1] Institute for Choice, University of South Australia Business School, Adelaide, Australia

[2] Centre for Health Economics, Monash Business School, Monash University, Melbourne, Australia

[3] Faculty of Health Sciences, School of Medicine, Flinders University, Adelaide, Australia

[4] Department of Paediatric Rehabilitation, Women's and Children's Hospital, Adelaide, Australia

*Corresponding Author:
Christine Mpundu-Kaambwa
Institute for Choice,
University of South Australia Business School,
Level 3 Way lee Building, North Terrace,
Adelaide SA 5001, Australia
Telephone: +61 8 8302 0228
Email: mpucc001@mymail.unisa.edu.au

Number of figures: 1

Number of references: 34

Word count: 2,122

Abstract word count: 300

Running title: Protocol for a systematic review of quality of life outcome measures for children with cerebral palsy

Keywords: cerebral palsy, quality of life, well-being, instruments, child

Funding sources/ sponsors: This systematic review protocol has received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest: All authors declare that they have no conflict of interest.

ABSTRACT

Introduction: Cerebral palsy is the most common cause of physical disability in children and adolescents and is associated with impairments that may reduce the quality of life (QOL) of this population. Patient reported outcome measures (PROMs) can facilitate the assessment of the effect of disease and treatment on QOL, from a patient viewpoint. The purpose of this systematic review is to identify PROMs that are used to measure QOL and subjective well-being (SWB) outcomes in young people with cerebral palsy and to evaluate the suitability of these PROMs for application in economic evaluations within this population.

Methods and analysis: MEDLINE, Scopus, the Cochrane Library, Web of Science, Econlit, PsycINFO, CINAHL, EMBASE, and informit will be systematically searched from inception to date of search. Published peer-reviewed, English language articles reporting PROMs measuring QOL or SWB outcomes in children and adolescents with cerebral palsy will be included. One reviewer will conduct the initial search and screen titles and abstracts for potentially eligible studies. To reduce the likelihood of reviewer selection bias, two other reviewers will independently screen a randomly selected sub-sample (10%) of the citations. Two reviewers will then retrieve full texts of potentially eligible studies and assess them against predefined inclusion criteria. The suitability of selected PROMS for use in economic evaluations of young people with cerebral palsy will be assessed using the International Society of Quality of Life Research (ISOQOL) recommended Minimum Standards and the Patient-Centered Outcomes and Comparative Effectiveness Research (CREATE) checklist. A narrative synthesis of extracted data will be presented including study descriptive data, PROMs measurement properties, settings in which they were applied and the valuation methods. Recommendations for practice on the selection of PROMs for use in economic evaluations of children and adolescents with cerebral palsy will be presented.

Ethics and dissemination: Ethical approval is not required as the proposed systematic review will not use primary data. The results of this study will be widely disseminated through publication in a peer-reviewed journal and conference presentation(s).

Systematic review registration number: International Prospective Register of Systematic Reviews (PROSPERO) number CRD42016049746.

Strength and limitations of this study

- The systematic review will produce a comprehensive assessment of existing PROMs (both preference-based and non-preferenced-based) that are used to assess QOL in children and young people with cerebral palsy.
- The systematic review will provide evidence on the suitability of preference-based PROMs for use within both trial and model-based economic evaluations of paediatric populations with cerebral palsy.
- The systematic review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO) and is reported in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.

INTRODUCTION

Patient reported outcome measures (PROMs) are increasingly being used in health services research to inform healthcare resource allocation decisions. [1, 2] PROMs assess a patient's subjective assessment of their well-being, health status or quality of life (QOL) at a single point in time and are collected via standardized, self-report questionnaires. [3, 4] PROMs may be differentiated into condition-specific and generic measures. Condition-specific measures are designed to assess health outcomes in people with specific medical conditions (e.g., the cerebral palsy quality of life [CP-QOL] questionnaire); whilst generic measures (e.g., the Pediatric Quality of Life Inventory [PedsQL]) are applicable across all disease areas. Condition-specific and generic measures can be subdivided into preference/utility-based and non-preference-based PROMs. Non-preference-based measures use a simple summative scoring system whereby individual items or dimensions are used to generate summary scores. [5] Preference-based PROMs typically incorporate scoring algorithms which are premised on preferences of general population samples for health states generated through valuation methods such as the standard gamble (SG) and time trade-off (TTO) techniques, and are usually anchored between 0 (representing death) to 1 (representing optimal health). Preference-based PROMs enable the calculation of quality adjusted life years (QALYs) for use in cost-utility analysis, a type of economic evaluation. [5-7] QALYs are a routinely used standard measure of benefit in economic evaluation.[8]

Cerebral palsy is a complex chronic disorder of motor impairment that requires long-term medical and supportive care services. It is the leading cause of physical disability in childhood with prevalence rates ranging between 2.0 and 3.5 per 1000 live births worldwide. [9] There are broad variations in the definition and classification of cerebral palsy. However, the International Executive Committee for the Definition of cerebral palsy, recommend the following definition: "Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy, and by secondary musculoskeletal problems". [10] As such, cerebral palsy has ubiquitous impacts on all aspects of a child's life. Cerebral palsy has been shown to have a negative effect on the QOL of children with the condition. [11, 12] The cost of care for persons with cerebral palsy in Australia was estimated

at AUD$43,431 per person per year in 2007 with the total annual national economic cost of cerebral palsy estimated at AUD$1.47 billion (of which approximately 37% was borne by the individual and/or their family). [13] Clearly, it is vital to consider the impact of the cost of long-term care on young people and /or their families. With these rising costs and competing healthcare demands, there is a growing need for optimal funding decisions. Economic evaluation is an important technique to help decision-makers determine the relative value for money of service innovations in health care and requires the robust measurement of appropriate health, health status, QOL or SWB outcomes [5]. This highlights the importance of finding appropriate PROMs for economic evaluation of services targeted at children and young people with this condition.

The World Health Organisation defines QOL as "an individual's perception of their position in life in the context of the culture and value system in which they live, and in relation to their goals, expectations, standards, and concern". [14] QOL is a broad concept which refers to the influence of all facets of an individual's life on their general well-being including HRQOL. HRQOL refers to an individual' self-perceived assessment of their health and its subsequent effect on their life and is defined as a subjective multi-dimensional construct of well-being and functioning based on physical, emotional, mental, social and behavioural features as perceived by patients. [15] In literature these two concepts, QOL and HRQOL are used interchangeably, [16] for the purposes of this systematic review both terms will be considered in the search strategy.

The main aim of this systematic review is to identify studies that have used PROMs to assess QOL and subjective well-being (SWB) in children with cerebral palsy and to evaluate the suitability of these PROMs for application in economic evaluations targeted at this population. Previous systematic reviews in cerebral palsy have focused on assessing performance of psychometric-based physical activity and/or participation measures [17, 18] and QOL [19-21]. These reviews did not distinguish between measures associated with different cerebral palsy health states. Further, only Janssens et al. [21] included preference-based outcome measures in their review even though the population was that of children and young people living with neurological disabilities and not exclusive to those with cerebral palsy. This current review may be distinguished from previous ones in three main ways:
Firstly, this review is focused exclusively on cerebral palsy and will capture the two year period beyond any previously conducted reviews. Secondly, the review will assess the

appropriateness of the PROMs applied for informing QOL associated with different cerebral palsy health states for the purposes of model-based economic evaluation. Thirdly, information on the settings in which the PROMs have been used will also be extracted and collated so as to determine the suitability of particular PROMs for particular settings.

The specific objectives of the review are:

1. To identify PROMs that are used to measure QOL and SWB outcomes in children and young people under the age of 18 years with cerebral palsy
2. To establish the different contexts in which the PROMs have been applied
3. To critically examine the suitability of preference-based PROMs for use within economic evaluations targeted at this population

Review questions

The proposed review will seek to address the following specific research questions:

1. What preference-based and non-preference-based PROMs are used to measure QOL and SWB outcomes in children and young people with cerebral palsy?
2. How suitable are the identified PROMs for use within economic evaluations of paediatric populations with cerebral palsy and in what contexts?

METHODS

Design

The protocol has been registered with International Prospective Register of Systematic Reviews (PROSPERO) registration number (CRD42016049746) and it has been developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.[22] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. [23]

The systematic review will follow a structured two-stage approach. Firstly, all PROMS (both preference-based and non-preference-based) and articles/studies reporting details of development and/or application of PROMs used to measure QOL and/or SWB in young people with cerebral palsy will be identified. Second, each of the PROMS identified will be

appraised using two checklists: The International Society of Quality of Life Research (ISOQOL) recommended Minimum Standards for Patient-Reported Outcome Measures,[24] and the Patient-Centered Outcomes and Comparative Effectiveness Research (CREATE) checklist for reporting valuation studies.[25] A University of South Australia Health Sciences Librarian with expertise in designing systematic reviews will be available to the team and will provide guidance on the search strategies for each database.

Eligibility criteria

Published, peer-reviewed, English-language articles reporting QOL and SWB outcomes of children and young people up to 18 years old with a diagnosis of cerebral palsy will be eligible for inclusion in the initial stage of the systematic review.

Inclusion criteria:

- The review will include all study designs in the preliminary search because it is expected that the number of preference-based PROMs in this field is relatively small;
- There will be no restrictions in terms of setting for the initial search because the literature in this field is likely to be relatively small and any restrictions at this stage over and above 'care-related' (rather than generic) would hinder any wider recommendations;
- Studies where PROMs were completed by either the child or parent (primary caregiver) will be included.

Exclusion criteria:

- Studies focused only on adults;
- Studies where the proxy respondent is not a parent or main caregiver (e.g. teacher, school principal, clinician);
- Studies where QOL and SWB data is on parents and caregivers of children with cerebral palsy;
- Publications that are not peer-reviewed including unpublished dissertations, reports, conference presentations, discussion papers and any grey literature.

Search strategy

An extensive search of the literature search will be conducted in nine electronic bibliographic databases from database inception to the date of the search: MEDLINE (including in-process

and other non- indexed citations viaOvid interface,); Scopus (via Elsevier interface); The Cochrane Library (including the Cochrane CENTRAL, EED and HTA); Web of Science Core Collection; Econlit (via Ovid interface); EMBASE (via Ovid interface; PsycINFO (via Ovid interface); CINAHL (via EBSCO-host); informit (via informit interface). The primary electronic search strategy was designed for MEDLINE and adapted as appropriate for each of the databases. The full search strategy is presented in the supplementary appendix. Key words and Medical Subject Headings (MeSH) terms include: "cerebral palsy", "children", "adolescents", "quality of life", "health related quality of life" and "well-being". To ensure that all significant literature is retrieved, both forward (inspecting articles in order to determine if key articles have been cited) and backward (examining reference lists) citation checking will be performed. Results from the search and retrieved references will be imported and managed in Thomson Reuters™ Endnote version X7.1 (2014) reference management software.

Selection process

First, all titles and abstracts of articles resulting from the search will be screened against the eligibility criteria independently by the lead review author (CMK), as has been done elsewhere. [26-28]The primary aim of screening is to identify articles that meet the inclusion criteria. Full texts will be retrieved at this initial stage only if the abstract contains limited information about the study and duplicate articles will be removed. To reduce the possibility of selection bias, two other authors (GC and EH) will independently screen 10% of all citations resulting from the search.[28] Cohen's Kappa statistic will be estimated to measure interrater reliability (degree of agreement) between the reviewers. [29-31] Cohen's Kappa statistic values less than or equal to 0 indicate no agreement, 0.01–0.20 (none to slight), 0.21–0.40 (fair), 0.41– 0.60 (moderate), 0.61–0.80 (substantial), and 0.81–1.00 (strong) agreement. If the interrater reliability is less than 0.80, i.e., strong level of agreement, [30] an additional subset of articles (25%) will be will be independently assessed. If the degree of agreement between the review authors is still less than 0.80, then the rest of the articles will be independently screened. Differences will be resolved by discussion and consultation with the review team. Second, full texts of potential candidate studies will be obtained and assessed for inclusion in the review. To ensure that all relevant literature is retrieved, both forward (inspecting in order to determine if key articles have been cited) and backward (examining reference lists) citation chasing will be performed. Where necessary, study authors will be contacted for clarification and additional information to inform study selection. Each stage of

the selection process will be outlined in a PRISMA-style flow chart and assessed against the 27 item PRISMA checklist.

Data collection

Summary data of each included PROM and article will be extracted into a data extraction form specifically designed for this review. Summary tables will be created in Microsoft Office Excel 2013 for (1) information about the candidate PROMs and (2) information pertaining to the identified studies. The information to be extracted from the included studies will be the following:

1. Descriptive information about study: date of publication; country of origin; sample size; study type and setting; study population and characteristics (including age and gender); study key results and conclusions

2. Descriptive information about the measure: name of PROM; domains/dimensions; number of items; description of the items; response method; method of administration); interpretation and summary scoring

3. Information about valuation of measure i.e. have preference weights been collected from a representative sample of children and adolescents with cerebral palsy? health states valued; preference elicitation method; population preference weights.

Two other reviewers will independently appraise the quality and suitability of the preference-based PROMs for measuring outcomes in paediatric populations with cerebral palsy. Any disagreements will be resolved by discussion and consultation with the review team. This evaluation will also follow ISOQOL checklist (for internal consistency reliability, test-retest reliability, content validity, construct validity, criterion validity, responsiveness, interpretability of scores, respondent burden and investigator burden) [24] and the CREATE checklist (for reporting valuation studies) to appraise the candidate utility-based PROMs. [25]

Data synthesis

A summary of included studies and PROMs will be presented in line with recommendations from the Cochrane Collaboration.[32] The main features of the included studies, instrument descriptions and contexts in which they are applied and information about valuation methods will be summarised into three tables.[33] Using this information, the suitability of each of the

PROMs identified for use in economic evaluation will be assessed and comparisons and disparities between instruments will be described.

Ethics and dissemination

The main aim of this review is to provide a systematic review of existing published literature and as such ethical approval to conduct this research is not required. This systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016049746) [34], registration number CRD42016049746. The findings of this review will be disseminated as a peer-reviewed journal article and will be presented at both national and international conferences.

Contributions

JR, RR, GC and CMK formulated the idea for the study. CMK wrote the first draft and the co-authors (EH, GC, RR, JR) revised the protocol for important intellectual content. CMK will act as a guarantor for the work.

Acknowledgements

CMK is supported by the Australian Government Research Training Program Scholarship.

References

1. National Institute for Health and Care Excellence., *Guide to the methods of technology appraisal* 2013, National Health Service.

2. Deshpande, P.R., et al., *Patient-reported outcomes: A new era in clinical research.* Perspect Clin Res, 2011. **2**(4): p. 137-44.

3. Acquadro, C., et al., *Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group meeting at the Food and Drug Administration, February 16, 2001.* Value Health, 2003. **6**(5): p. 522-31.

4. Willke, R.J., L.B. Burke, and P. Erickson, *Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels.* Control Clin Trials, 2004. **25**(6): p. 535-52.

5. Brazier J, et al., *Measuring and Valuing Health Benefits for Economic Evaluation.* 2007, London: Oxford University Press.

6. Drummond, M.F., et al., *Methods for the economic evaluation of health care programme. Third edition*. 2005.

7. Neumann, P.J., S.J. Goldie, and M.C. Weinstein, *Preference-Based Measures in Economic Evaluation in Health Care.* Annual Review of Public Health, 2000. **21**(1 1): p. 587-611.

8. Brazier, J.E., S. Dixon, and J. Ratcliffe, *The role of patient preferences in cost-effectiveness analysis: a conflict of values?* Pharmacoeconomics, 2009. **27**(9): p. 705-12.

9. Colver, A., C. Fairhurst, and P.O. Pharoah, *Cerebral palsy.* Lancet, 2014. **383**(9924): p. 1240-9.

10. Rosenbaum, P., et al., *A report: the definition and classification of cerebral palsy April 2006.* Dev Med Child Neurol Suppl, 2007. **109**: p. 8-14.

11. Russo, R.N., et al., *Self-esteem, self-concept, and quality of life in children with hemiplegic cerebral palsy.* J Pediatr, 2008. **153**(4): p. 473-7.

12. Livingston, M.H., et al., *Quality of life among adolescents with cerebral palsy: what does the literature tell us?* Dev Med Child Neurol, 2007. **49**(3): p. 225-31.

13. Access Economics, *The Economic Impact of Cerebral Palsy in Australia in 2007, Report for CP Australia*. 2008.

14. *The World Health Organization quality of life assessment (WHOQOL): Position paper from the World Health Organization.* Social Science & Medicine, 1995. **41**(10): p. 1403-1409.

15. Ravens-Sieberer, U., et al., *Generic health-related quality-of-life assessment in children and adolescents: methodological considerations.* Pharmacoeconomics, 2006. **24**(12): p. 1199-220.

16. Karimi, M. and J. Brazier, *Health, Health-Related Quality of Life, and Quality of Life: What is the Difference?* Pharmacoeconomics, 2016. **34**(7): p. 645-649.

17. Harvey, A., et al., *A systematic review of measures of activity limitation for children with cerebral palsy.* Dev Med Child Neurol, 2008. **50**(3): p. 190-8.

18. Morris, C., J.J. Kurinczuk, and R. Fitzpatrick, *Child or family assessed measures of activity performance and participation for children with cerebral palsy: a structured review.* Child Care Health Dev, 2005. **31**(4): p. 397-407.

19. Davis, E., et al., *Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes.* Dev Med Child Neurol, 2006. **48**(4): p. 311-8.

20. Carlon, S., et al., *A systematic review of the psychometric properties of Quality of Life measures for school aged children with cerebral palsy.* BMC Pediatr, 2010. **10**: p. 81.

21. Janssens, A., et al., *Measurement properties of multidimensional patient-reported outcome measures in neurodisability: a systematic review of evaluation studies.* Dev Med Child Neurol, 2016. **58**(5): p. 437-51.

22. Shamseer, L., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration & explanation.* BMJ, 2015. **349**.

23. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* PLoS Med, 2009. **6**.

24. Reeve, B.B., et al., *ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research.* Qual Life Res, 2013. **22**(8): p. 1889-905.

25. Xie, F., et al., *A Checklist for Reporting Valuation Studies of Multi-Attribute Utility-Based Instruments (CREATE).* Pharmacoeconomics, 2015. **33**(8): p. 867-77.

26. Bhattarai, N., et al., *Economic evaluations on centralisation of specialised healthcare services: a systematic review of methods.* BMJ Open, 2016. **6**(5).

27. Kigozi, J., et al., *Estimating productivity costs using the friction cost approach in practice: a systematic review.* The European Journal of Health Economics, 2016. **17**(1): p. 31-44.

28. Mccaffrey, N., et al., *Protocol for a systematic review of preference-based instruments for measuring care-related outcomes and their suitability for the palliative care setting.* BMJ open, 2016. **6**(9): p. e012181.

29. Cohen, J., *A Coefficient of Agreement for Nominal Scales.* Educational and Psychological Measurement, 1960. **20**(1): p. 37-46.

30. Orwin., E.G., *Evaluating coding decisions*, in *The Handbook of Research Synthesis*, L.H. Cooper H, Editor. 1994, Russell Sage Foundation: New York.

31. McHugh, M.L., *Interrater reliability: the kappa statistic.* Biochemia Medica, 2012. **22**(3): p. 276-282.

32. Ryan, R., Cochrance Consumers and Communication Review Group. *Cochrance Consumers and Communication Review Group: data synthesis and analysis*. 2013.

33. Green, B.N., C.D. Johnson, and A. Adams, *Writing narrative literature reviews for peer-reviewed journals: secrets of the trade.* Journal of Chiropractic Medicine, 2006. **5**(3): p. 101-117.

34. Mpundu-Kaambwa, C.H., E.; Chen, G.; Russo, R.; Ratcliffe, J. *A systematic review of quality of life outcome measures for children with cerebral palsy*. PROSPERO International prospective register of systematic reviews, 2016.

Appendix I: MEDLINE search strategy

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present. Includes subsets: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily

#	Searches
1	Cerebral Palsy/
2	(Cerebral pals* or CP or spastic diplegia* or little disease or little's disease or hemiplegia or quadriplegia).tw,kw .
3	1 or 2
4	adolescent/ or child/
5	(Child* or adolescen* or teen* or pediatric* or paediatric* or youth or young * toddler or infant).tw,kw.
6	4 or 5
7	"Quality of Life"/ or quality-adjusted life years/
8	("quality of life" or QoL or HRQoL or HRQL or HRQOL or QL or health related QOL or hql or hqol or h-qol or hr-qol or quality adjusted life or qaly* or qald* or qale* or qtime* or disability adjusted life or daly* or health utilit* or health outcomes or patient outcome or functioning or activit* or participation or health status or functional status).tw,kw .
9	(Quality adj2 (well-being or wellbeing)).tw,kw.
10	qwb.tw,kw.
11	or/7-10
12	3 and 6 and 11
13	"surveys and questionnaires"/ or self-report/
14	(Instrument* or tool* or measure* or test* or dimension* or multidimension* or scale* or rating* or item response or properties or domain* or psychometric* or modified or schedule* or evaluat* or classification* or inventor* or index or indice* or scale* or question* or form or valid* reliab* assess* repeatability or acceptability or responsiveness or feasibility or PROM or child report or self-assess* or preference-based instrument or multi-attribute utility cost utility).tw,kw .
15	13 or 14
16	12 and 15
17	limit 16 to English language

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	1
Sponsor	5b	Provide name for the review funder and/or sponsor	1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	1
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8,14

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Protocol for a systematic review of instruments for the assessment of quality of life and well-being in children and adolescents with cerebral palsy

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-015924.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Jun-2017
Complete List of Authors:	Mpundu-Kaambwa, Christine; University of South Australia, Business School Chen, Gang; Monash University, Centre for Health Economics Huynh , Elisabeth; University of South Australia, Business School Russo, Remo; Women's and Children's Hospital Adelaide, Paediatric Rehabilitation Ratcliffe, Julie; University of South Australia, Institute for Choice, Unisa Business School
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Paediatrics, Neurology, Qualitative research
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Developmental neurology & neurodisability < PAEDIATRICS, Quality of life, Cerebral Palsy, Child, Preference-based-instruments

Protocol for a systematic review of instruments for the assessment of quality of life and well-being in children and adolescents with cerebral palsy

Authors: Christine Mpundu-Kaambwa[1*], Gang Chen[2], Elisabeth Huynh[1], Remo Russo[3,4], Julie Ratcliffe[1]

[1] Institute for Choice, University of South Australia Business School, Adelaide, Australia

[2] Centre for Health Economics, Monash Business School, Monash University, Melbourne, Australia

[3] Faculty of Health Sciences, School of Medicine, Flinders University, Adelaide, Australia

[4] Department of Paediatric Rehabilitation, Women's and Children's Hospital, Adelaide, Australia

*Corresponding Author:
Christine Mpundu-Kaambwa
Institute for Choice,
University of South Australia Business School,
Level 3 Way lee Building, North Terrace,
Adelaide SA 5001, Australia
Telephone: +61 8 8302 0228
Email: christine.mpundu-kaambwa@unisa.edu.au

Number of tables: 1

Number of references: 43

Word count: 2,653

Abstract word count: 300

Running title: Protocol for a systematic review of quality of life outcome measures for children with cerebral palsy

Keywords: cerebral palsy, quality of life, well-being, instruments, child

Funding sources/ sponsors: This systematic review protocol has received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest: All authors declare that they have no conflict of interest.

ABSTRACT

Introduction: Cerebral palsy is the most common cause of physical disability in children and adolescents and is associated with impairments that may reduce the quality of life (QOL) of this population. Patient reported outcome measures (PROMs) can facilitate the assessment of the effect of disease and treatment on QOL, from a patient viewpoint. The purpose of this systematic review is to identify PROMs that are used to measure QOL and subjective well-being (SWB) outcomes in young people with cerebral palsy and to evaluate the suitability of these PROMs for application in economic evaluations within this population.

Methods and analysis: MEDLINE, Scopus, the Cochrane Library, Web of Science, Econlit, PsycINFO, CINAHL, EMBASE, and informit will be systematically searched from inception to date of search. Published peer-reviewed, English language articles reporting PROMs measuring QOL or SWB outcomes in children and adolescents with cerebral palsy will be included. One reviewer will conduct the initial search and screen titles and abstracts for potentially eligible studies. To reduce the likelihood of reviewer selection bias, two other reviewers will independently screen a randomly selected sub-sample (10%) of the citations. Two reviewers will then retrieve full texts of potentially eligible studies and assess them against predefined inclusion criteria. The suitability of selected PROMS for use in economic evaluations of young people with cerebral palsy will be assessed using the International Society of Quality of Life Research (ISOQOL) recommended Minimum Standards and the Patient-Centered Outcomes and Comparative Effectiveness Research (CREATE) checklist. A narrative synthesis of extracted data will be presented including study descriptive data, PROMs measurement properties, settings in which they were applied and the valuation methods. Recommendations for practice on the selection of PROMs for use in economic evaluations of children and adolescents with cerebral palsy will be presented.

Ethics and dissemination: Ethical approval is not required as the proposed systematic review will not use primary data. The results of this study will be widely disseminated through publication in a peer-reviewed journal and conference presentation(s).

Systematic review registration number: International Prospective Register of Systematic Reviews (PROSPERO) number CRD42016049746.

Strength and limitations of this study

- The systematic review will identify PROMs used to measure QOL and SWB in young people with cerebral palsy aged 0-18 years.
- The systematic review will establish the different contexts in which the PROMs have been applied.
- The systematic review will produce a comprehensive assessment of existing PROMs (both preference-based and non-preference-based) that are used to assess QOL in children and young people with cerebral palsy.
- The systematic review will provide evidence on the suitability of preference-based PROMs for use within both trial and model-based economic evaluations of paediatric populations with cerebral palsy.
- A limitation of this systematic review is the exclusion of studies that are not published in English, which may mean that we miss some articles examining quality of life outcomes in young people with cerebral palsy in non-English speaking countries.

INTRODUCTION

Patient reported outcome measures (PROMs) are increasingly being used in health services research to inform healthcare resource allocation decisions. [1, 2] PROMs assess a patient's subjective assessment of their well-being, health status or quality of life (QOL) at a single point in time and are collected via standardized, self-report questionnaires. [3, 4] PROMs may be differentiated into condition-specific and generic measures. Condition-specific measures are designed to assess health outcomes in people with specific medical conditions (e.g., the cerebral palsy quality of life [CP-QOL] questionnaire); whilst generic measures (e.g., the Pediatric Quality of Life Inventory [PedsQL]) are applicable across all disease areas. Condition-specific and generic measures can be subdivided into preference/utility-based and non-preference-based PROMs. Non-preference-based measures use a simple summative scoring system whereby individual items or dimensions are used to generate summary scores. [5]Preference-based PROMs typically incorporate scoring algorithms which are premised on preferences of general population samples for health states generated through valuation methods such as the standard gamble (SG) and time trade-off (TTO) techniques, and are usually anchored between 0 (representing death) to 1 (representing optimal health). Preference-based PROMs enable the calculation of quality adjusted life years (QALYs) for use in cost-utility analysis, a type of economic evaluation.[5-7] QALYs are a routinely used standard measure of benefit in economic evaluation.[8]

Cerebral palsy is a complex chronic disorder of motor impairment that requires long-term medical and supportive care services. It is the leading cause of physical disability in childhood with prevalence rates ranging between 2.0 and 3.5 per 1000 live births worldwide. [9] There are broad variations in the definition and classification of cerebral palsy. However, the International Executive Committee for the Definition of cerebral palsy, recommend the following definition: "Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy, and by secondary musculoskeletal problems". [10] As such, cerebral palsy has ubiquitous impacts on all aspects of a child's life. Cerebral palsy has been shown to have a negative effect on the QOL of children with the condition. [11, 12] The cost of care for persons with cerebral palsy in Australia was estimated

at AUD$43,431 per person per year in 2007 with the total annual national economic cost of cerebral palsy estimated at AUD$1.47 billion (of which approximately 37% was borne by the individual and/or their family). [13] In the United States of America in 2005, the total Medicaid expenditures averaged $43,338 for a child with cerebral palsy [14] and the average lifetime cost of cerebral palsy (based on 2003 US dollars) was estimated to be $921,000 per person of which 81% are indirect costs and 19% are direct costs. [15] In 2007, a Dutch study on children with cerebral palsy, found the annual cost to be €40,265 per child.[16] Clearly, it is vital to consider the impact of the cost of long-term care on young people and /or their families. With these rising costs and competing healthcare demands, there is a growing need for optimal funding decisions. Economic evaluation is an important technique to help decision-makers determine the relative value for money of service innovations in health care and requires the robust measurement of appropriate health, health status, QOL or subjective well-being (SWB) outcomes [17]. This highlights the importance of finding appropriate PROMs for economic evaluation of services targeted at children and young people with this condition.

The World Health Organisation defines QOL as "an individual's perception of their position in life in the context of the culture and value system in which they live, and in relation to their goals, expectations, standards, and concern". [18] QOL is a broad concept which refers to the influence of all facets of an individual's life on their general well-being including HRQOL. HRQOL refers to an individual' self-perceived assessment of their health and its subsequent effect on their life and is defined as a subjective multi-dimensional construct of well-being and functioning based on physical, emotional, mental, social and behavioural features as perceived by patients. [19] In literature these two concepts, QOL and HRQOL are used interchangeably, [20] for the purposes of this systematic review both terms will be considered in the search strategy.

The main aim of this systematic review is to identify studies that have used PROMs to assess QOL and SWB in children with cerebral palsy and to evaluate the suitability of these PROMs for application in economic evaluations targeted at this population. Previous systematic reviews in cerebral palsy have focused on assessing performance of psychometric-based physical activity and/or participation measures [21, 22] and QOL [23-25]. These reviews did not distinguish between measures associated with different cerebral palsy health states depicting the levels of severity as classified using a number of metrics including gross motor

function [26] manual ability [27] and communication [28].” Further, only Janssens et al. [25] included preference-based outcome measures in their review even though the population was that of children and young people living with neurological disabilities and not exclusive to those with cerebral palsy. This current review may be distinguished from previous ones in three main ways:

Firstly, this review is focused exclusively on cerebral palsy. Secondly, the review will assess the appropriateness of the PROMs applied for informing QOL associated with different cerebral palsy health states for the purposes of model-based economic evaluation. Thirdly, information on the contexts in which the PROMs have been used will also be extracted and collated so as to determine the suitability of particular PROMs for particular settings (with context defined according to the functional ability of populations as measured by the Gross Motor Function Classification System (GMFCS) [26], in which the instruments have been used)

The specific objectives of the review are:

1. To identify PROMs that are used to measure QOL and SWB outcomes in children and young people aged 0-18 years with cerebral palsy
2. To establish the different contexts in which the PROMs have been applied
3. To critically examine the suitability of preference-based PROMs for use within economic evaluations targeted at this population

Review questions

The proposed review will seek to address the following specific research questions:

1. What preference-based and non-preference-based PROMs are used to measure QOL and SWB outcomes in children and young people with cerebral palsy?
2. How suitable are the identified PROMs for use within economic evaluations of paediatric populations with cerebral palsy and in what contexts?

METHODS

Design

The protocol has been registered with International Prospective Register of Systematic Reviews (PROSPERO) registration number (CRD42016049746) and it has been developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.[29] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. [30]

The systematic review will follow a structured two-stage approach. Firstly, all PROMS (both preference-based and non-preference-based) and articles/studies reporting details of development and/or application of PROMs used to measure QOL and/or SWB in young people with cerebral palsy will be identified. Second, each of the PROMS identified will be appraised using two checklists: The International Society of Quality of Life Research (ISOQOL) recommended Minimum Standards for Patient-Reported Outcome Measures,[31] and the Patient-Centered Outcomes and Comparative Effectiveness Research (CREATE) checklist for reporting valuation studies.[32] The ISOQOL was included for purposes of appraising non-preference-based and CREATE will be used to appraise the candidate utility-based (preference-based) PROMs. A University of South Australia Health Sciences Librarian with expertise in designing systematic reviews will be available to the team and will provide guidance on the search strategies for each database.

Eligibility criteria

Published, peer-reviewed, English-language articles reporting QOL and SWB outcomes of children and young people aged 0-18 years with a diagnosis of cerebral palsy will be eligible for inclusion in the initial stage of the systematic review.

There is currently no consensus regarding the inclusion or exclusion of non-English language articles to systematic reviews. Some authors seem to suggest that excluding non-English language studies from systematic reviews may lead to language-bias and subsequently lead to inaccurate conclusions. However, other studies have reported results contrary to this which suggest that restricting searches to the English language does not alter the outcome of systematic reviews and meta-analyses [33, 34]. This is more so true in clinical fields which have a high prevalence of English language articles and research.

Inclusion criteria:

- The review will include all study designs in the preliminary search because it is expected that the number of preference-based PROMs in this field is relatively small;

- There will be no restrictions in terms of setting for the initial search because the literature in this field is likely to be relatively small and any restrictions at this stage over and above 'care-related' (rather than generic) would hinder any wider recommendations;
- To allow for a relatively broader definition of carers beyond primary carers, studies where PROMs were completed by either, the child, parent (primary caregiver), clinician, teachers or school principal etc. will be included.
- Both preference and non-preference instruments will be included as well as generic and condition specific instruments.

Exclusion criteria:

- Studies focused only on adults. Studies that examine participants across both child/adolescent and adult age ranges will only be included if majority of the sample are children/adolescent and 0-18yrs and if results are for the two categories reported separately
- Studies where QOL and SWB data is on parents and caregivers of children with cerebral palsy;
- Publications that are not peer-reviewed including unpublished dissertations, reports, conference presentations, discussion papers and any grey literature. This is so as to ensure that only articles that have gone through the rigorous review and editorial process are included.

Search strategy

An extensive search of the literature search will be conducted in nine electronic bibliographic databases from database inception to the date of the search: MEDLINE (including in-process and other non- indexed citations viaOvid interface,); Scopus (via Elsevier interface); The Cochrane Library (including the Cochrane CENTRAL, EED and HTA); Web of Science Core Collection; Econlit (via Ovid interface); EMBASE (via Ovid interface; PsycINFO (via Ovid interface); CINAHL (via EBSCO-host); informit (via informit interface). The primary electronic search strategy was designed for MEDLINE and adapted as appropriate for each of the databases. The full search strategy is presented in the supplementary appendix. Key words and Medical Subject Headings (MeSH) terms include: "cerebral palsy", "children", "adolescents", "quality of life", "health related quality of life" and "well-being". To ensure that all significant literature is retrieved, both forward (inspecting articles in order to

determine if key articles have been cited) and backward (examining reference lists) citation checking will be performed on all full texts examined so as to ensure that no eligible studies are missed out. Results from the search and retrieved references will be imported and managed in Thomson Reuters™ Endnote version X7.1 (2014) reference management software.

Selection process

First, all titles and abstracts of articles resulting from the search will be screened against the eligibility criteria independently by the lead review author (CMK), as has been done elsewhere. [35-37] The primary aim of screening is to identify articles that meet the inclusion criteria. Full texts will be retrieved at this initial stage only if the abstract contains limited information about the study and duplicate articles will be removed. To reduce the possibility of selection bias, a randomly selected subset of citations (20%) will be independently assessed by two other members of the review team (GC and EH)..[37] Cohen's Kappa statistic will be estimated to measure interrater reliability (degree of agreement) between the reviewers. [38-40] Cohen's Kappa statistic values less than or equal to 0 indicate no agreement, 0.01–0.20 (none to slight), 0.21–0.40 (fair), 0.41– 0.60 (moderate), 0.61–0.80 (substantial), and 0.81–1.00 (strong) agreement. If the interrater reliability is less than 0.80, i.e., strong level of agreement, [39] an additional subset of articles (25%) will be will be independently assessed. If the degree of agreement between the review authors is still less than 0.80, then the rest of the articles will be independently screened. Differences will be resolved by discussion and consultation with the review team. Second, full texts of potential candidate studies will be obtained and assessed for inclusion in the review. To ensure that all relevant literature is retrieved, both forward (inspecting in order to determine if key articles have been cited) and backward (examining reference lists) citation chasing will be performed. Where necessary, study authors will be contacted for clarification and additional information to inform study selection. Each stage of the selection process will be outlined in a PRISMA-style flow chart and assessed against the 27 item PRISMA checklist.

Data collection

Summary data of each included PROM and article will be extracted into a data extraction form specifically designed for this review. Summary tables will be created in Microsoft Office Excel 2013 for (1) information about the candidate PROMs and (2) information

pertaining to the identified studies. The information to be extracted from the included studies will be the following:

1. Descriptive information about study: date of publication; country of origin; sample size; study type and setting; study population and characteristics (including age, gender and Gross Motor Functioning Classification System); study key results and conclusions.

2. Descriptive information about the measure: name of PROM; domains/dimensions; number of items; description of the items; response method; method of administration; interpretation and summary scoring.

3. Information about valuation of measure i.e. have preference weights been collected from a representative sample of children and adolescents with cerebral palsy? health states valued; preference elicitation method; population preference weights.

Two other reviewers will independently appraise the quality and suitability of the preference-based PROMs for measuring outcomes in paediatric populations with cerebral palsy. Any disagreements will be resolved by discussion and consultation with the review team. This evaluation will also follow ISOQOL checklist (for internal consistency reliability, test-retest reliability, content validity, construct validity, criterion validity, responsiveness, interpretability of scores, respondent burden and investigator burden) [31] and the CREATE checklist (for reporting valuation studies) to appraise the candidate utility-based PROMs. [32]

Data synthesis

A summary of included studies and PROMs will be presented in line with recommendations from the Cochrane Collaboration.[41] The main features of the included studies, instrument descriptions and contexts in which they are applied and information about valuation methods will be summarised into three tables.[42] Using this information, the suitability of each of the PROMs identified for use in economic evaluation will be assessed and comparisons and disparities between instruments will be described.

Discussion

To the best of our knowledge, this is first systematic review that will comprehensively assess existing PROMs (both preference-based and non-preference-based) that are used to measure QOL in children and young people with cerebral palsy. Multiple bibliographic databases will be systematically searched from inception to date of search. This review will advance the field of health economics research in the following ways: First, the review will identify PROMs used to measure QOL and SWB in young people with cerebral palsy aged 0-18 years. Second, the review will establish the different contexts in which the PROMs have been applied. Third, the systematic review will provide evidence on the suitability of preference-based PROMs for use within both trial and model-based economic evaluations of paediatric populations with cerebral palsy.

A limitation of this systematic review is the exclusion of studies that are not published in English, which may mean that we miss some articles examining quality of life outcomes in young people with cerebral palsy in non-English speaking countries. However based on results of previous reviews [22, 24, 25] in this field as well as expertise and research experience of the research team, we do not anticipate a large number of non-English articles in this field and are therefore confident that no significant difference will be made by excluding them.

Ethics and dissemination

The main aim of this review is to provide a systematic review of existing published literature and as such ethical approval to conduct this research is not required. This systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016049746) [43], registration number CRD42016049746. The findings of this review will be disseminated as a peer-reviewed journal article and will be presented at both national and international conferences.

Contributions

JR, RR, GC and CMK formulated the idea for the study. CMK wrote the first draft and the co-authors (EH, GC, RR, JR) revised the protocol for important intellectual content. CMK will act as a guarantor for the work.

Acknowledgements

CMK is supported by the Australian Government Research Training Program Scholarship.

References

1. National Institute for Health and Care Excellence NICE. *Guide to the methods of technology appraisal 2013*. 2013.

2. Deshpande, P.R., et al., *Patient-reported outcomes: A new era in clinical research.* Perspect Clin Res, 2011. **2**(4): p. 137-44.

3. Acquadro, C., et al., *Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group meeting at the Food and Drug Administration, February 16, 2001.* Value Health, 2003. **6**(5): p. 522-31.

4. Willke, R.J., L.B. Burke, and P. Erickson, *Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels.* Control Clin Trials, 2004. **25**(6): p. 535-52.

5. Brazier, J., Ratcliffe, J. Salmon, J, A. and A. Tsuchiya, *Measuring and Valuing Health Benefits for Economic Evaluation*. 2017, London: Oxford University Press.

6. Drummond MF, S.M., Torrance GW, O'Brien BJ, Stoddart GL. , *Methods for the Economic Evaluation of Health Care Programmes*. 2005, Oxford: Oxford University Press.

7. Neumann, P.J., S.J. Goldie, and M.C. Weinstein, *Preference-Based Measures in Economic Evaluation in Health Care.* Annual Review of Public Health, 2000. **21**(1 1): p. 587-611.

8. Brazier, J.E., S. Dixon, and J. Ratcliffe, *The role of patient preferences in cost-effectiveness analysis: a conflict of values?* Pharmacoeconomics, 2009. **27**(9): p. 705-12.

9. Colver, A., C. Fairhurst, and P.O. Pharoah, *Cerebral palsy.* Lancet, 2014. **383**(9924): p. 1240-9.

10. Rosenbaum, P., et al., *A report: the definition and classification of cerebral palsy April 2006.* Dev Med Child Neurol Suppl, 2007. **109**: p. 8-14.

11. Russo, R.N., et al., *Self-esteem, self-concept, and quality of life in children with hemiplegic cerebral palsy.* J Pediatr, 2008. **153**(4): p. 473-7.

12. Livingston, M.H., et al., *Quality of life among adolescents with cerebral palsy: what does the literature tell us?* Dev Med Child Neurol, 2007. **49**(3): p. 225-31.

13. Access Economics, *The Economic Impact of Cerebral Palsy in Australia in 2007, Report for CP Australia*. 2008, Access Economics: Canberra, Australia.

14. Kancherla, V., et al., *Medical expenditures attributable to cerebral palsy and intellectual disability among Medicaid-enrolled children.* Res Dev Disabil, 2012. **33**(3): p. 832-40.

15. Centers for Disease Control and Prevention., *Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment--United States, 2003.* MMWR Morb Mortal Wkly Rep, 2004. **53**(3): p. 57-9.

16. Hoving, M.A., et al., *Intractable spastic cerebral palsy in children: a Dutch cost of illness study.* Dev Med Child Neurol, 2007. **49**(5): p. 397-8.

17. Brazier J, et al., *Measuring and Valuing Health Benefits for Economic Evaluation.* 2007, London: Oxford University Press.

18. *The World Health Organization quality of life assessment (WHOQOL): Position paper from the World Health Organization.* Social Science & Medicine, 1995. **41**(10): p. 1403-1409.

19. Ravens-Sieberer, U., et al., *Generic health-related quality-of-life assessment in children and adolescents: methodological considerations.* Pharmacoeconomics, 2006. **24**(12): p. 1199-220.

20. Karimi, M. and J. Brazier, *Health, Health-Related Quality of Life, and Quality of Life: What is the Difference?* Pharmacoeconomics, 2016. **34**(7): p. 645-649.

21. Harvey, A., et al., *A systematic review of measures of activity limitation for children with cerebral palsy.* Dev Med Child Neurol, 2008. **50**(3): p. 190-8.

22. Morris, C., J.J. Kurinczuk, and R. Fitzpatrick, *Child or family assessed measures of activity performance and participation for children with cerebral palsy: a structured review.* Child Care Health Dev, 2005. **31**(4): p. 397-407.

23. Davis, E., et al., *Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes.* Dev Med Child Neurol, 2006. **48**(4): p. 311-8.

24. Carlon, S., et al., *A systematic review of the psychometric properties of Quality of Life measures for school aged children with cerebral palsy.* BMC Pediatr, 2010. **10**: p. 81.

25. Janssens, A., et al., *Measurement properties of multidimensional patient-reported outcome measures in neurodisability: a systematic review of evaluation studies.* Dev Med Child Neurol, 2016. **58**(5): p. 437-51.

26. Palisano, R., et al., *Development and reliability of a system to classify gross motor function in children with cerebral palsy.* Dev Med Child Neurol, 1997. **39**(4): p. 214-23.

27. Eliasson, A.C., et al., *The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability.* Dev Med Child Neurol, 2006. **48**(7): p. 549-54.

28. Hidecker, M.J., et al., *Developing and validating the Communication Function Classification System for individuals with cerebral palsy.* Dev Med Child Neurol, 2011. **53**(8): p. 704-10.

29. Shamseer, L., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration & explanation.* BMJ, 2015. **349**.

30. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* PLoS Med, 2009. **6**.

31. Reeve, B.B., et al., *ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research.* Qual Life Res, 2013. **22**(8): p. 1889-905.

32. Xie, F., et al., *A Checklist for Reporting Valuation Studies of Multi-Attribute Utility-Based Instruments (CREATE).* Pharmacoeconomics, 2015. **33**(8): p. 867-77.

33. Morrison, A., et al., *The effect of English-Language restriction on systematic review-based meta-analyses: A systematic review of emipirical studies.* International Journal of Technology Assessment in Health Care, 2012. **28**(2): p. 138-144.

34. Moher, D., et al., *The inclusion of reports of randomised trials published in languages other than English in systematic reviews.* Health Technol Assess, 2003. **7**(41): p. 1-90.

35. Bhattarai, N., et al., *Economic evaluations on centralisation of specialised healthcare services: a systematic review of methods.* BMJ Open, 2016. **6**(5).

36. Kigozi, J., et al., *Estimating productivity costs using the friction cost approach in practice: a systematic review.* The European Journal of Health Economics, 2016. **17**(1): p. 31-44.

37. Mccaffrey, N., et al., *Protocol for a systematic review of preference-based instruments for measuring care-related outcomes and their suitability for the palliative care setting.* BMJ open, 2016. **6**(9): p. e012181.

38. Cohen, J., *A Coefficient of Agreement for Nominal Scales.* Educational and Psychological Measurement, 1960. **20**(1): p. 37-46.

39. Orwin., E.G., *Evaluating coding decisions*, in *The Handbook of Research Synthesis*, L.H. Cooper H, Editor. 1994, Russell Sage Foundation: New York.

40. McHugh, M.L., *Interrater reliability: the kappa statistic.* Biochemia Medica, 2012. **22**(3): p. 276-282.

41. Ryan R. *'Cochrane Consumers and Communication Group: meta-analysis*. December 2016. DOI: http://cccrg.cochrane.org.

42. Green, B.N., C.D. Johnson, and A. Adams, *Writing narrative literature reviews for peer-reviewed journals: secrets of the trade.* Journal of Chiropractic Medicine, 2006. **5**(3): p. 101-117.

43. Mpundu-Kaambwa, C.H., E.; Chen, G.; Russo, R.; Ratcliffe, J. *A systematic review of quality of life outcome measures for children with cerebral palsy*. PROSPERO International prospective register of systematic reviews, 2016.

Appendix I: MEDLINE search strategy

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present. Includes subsets: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily

#	Searches
1	Cerebral Palsy/
2	(Cerebral pals* or CP or spastic diplegia* or little disease or little's disease or hemiplegia or quadriplegia).tw,kw .
3	1 or 2
4	adolescent/ or child/
5	(Child* or adolescen* or teen* or pediatric* or paediatric* or youth or young * toddler or infant).tw,kw.
6	4 or 5
7	"Quality of Life"/ or quality-adjusted life years/
8	("quality of life" or QoL or HRQoL or HRQL or HRQOL or QL or health related QOL or hql or hqol or h-qol or hr-qol or quality adjusted life or qaly* or qald* or qale* or qtime* or disability adjusted life or daly* or health utilit* or health outcomes or patient outcome or functioning or activit* or participation or health status or functional status).tw,kw .
9	(Quality adj2 (well-being or wellbeing)).tw,kw.
10	qwb.tw,kw.
11	or/7-10
12	3 and 6 and 11
13	"surveys and questionnaires"/ or self-report/
14	(Instrument* or tool* or measure* or test* or dimension* or multidimension* or scale* or rating* or item response or properties or domain* or psychometric* or modified or schedule* or evaluat* or classification* or inventor* or index or indice* or scale* or question* or form or valid* reliab* assess* repeatability or acceptability or responsiveness or feasibility or PROM or child report or self-assess* or preference-based instrument or multi-attribute utility cost utility).tw,kw .
15	13 or 14
16	12 and 15
17	limit 16 to English language

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	1
Sponsor	5b	Provide name for the review funder and/or sponsor	1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	1
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8,14

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Protocol for a systematic review of instruments for the assessment of quality of life and well-being in children and adolescents with cerebral palsy

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-015924.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Aug-2017
Complete List of Authors:	Mpundu-Kaambwa, Christine; University of South Australia, Business School Chen, Gang; Monash University, Centre for Health Economics Huynh , Elisabeth; University of South Australia, Business School Russo, Remo; Women's and Children's Hospital Adelaide, Paediatric Rehabilitation Ratcliffe, Julie; University of South Australia, Institute for Choice, Unisa Business School
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Paediatrics, Neurology, Qualitative research
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Developmental neurology & neurodisability < PAEDIATRICS, Quality of life, Cerebral Palsy, Child, Preference-based-instruments

Protocol for a systematic review of instruments for the assessment of quality of life and well-being in children and adolescents with cerebral palsy

Authors: Christine Mpundu-Kaambwa[1*], Gang Chen[2], Elisabeth Huynh[1], Remo Russo[3,4], Julie Ratcliffe[1]

[1] Institute for Choice, University of South Australia Business School, Adelaide, Australia

[2] Centre for Health Economics, Monash Business School, Monash University, Melbourne, Australia

[3] Faculty of Health Sciences, School of Medicine, Flinders University, Adelaide, Australia

[4] Department of Paediatric Rehabilitation, Women's and Children's Hospital, Adelaide, Australia

*Corresponding Author:
Christine Mpundu-Kaambwa
Institute for Choice,
University of South Australia Business School,
Level 3 Way lee Building, North Terrace,
Adelaide SA 5001, Australia
Telephone: +61 8 8302 0228
Email: christine.mpundu-kaambwa@unisa.edu.au

Number of tables: 1

Number of references: 43

Word count: 2,653

Abstract word count: 300

Running title: Protocol for a systematic review of quality of life outcome measures for children with cerebral palsy

Keywords: cerebral palsy, quality of life, well-being, instruments, child

Funding sources/ sponsors: This systematic review protocol has received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest: All authors declare that they have no conflict of interest.

ABSTRACT

Introduction: Cerebral palsy is the most common cause of physical disability in children and adolescents and is associated with impairments that may reduce the quality of life (QOL) of this population. Patient reported outcome measures (PROMs) can facilitate the assessment of the effect of disease and treatment on QOL, from a patient viewpoint. The purpose of this systematic review is to identify PROMs that are used to measure QOL and subjective well-being (SWB) outcomes in young people with cerebral palsy and to evaluate the suitability of these PROMs for application in economic evaluations within this population.

Methods and analysis: MEDLINE, Scopus, the Cochrane Library, Web of Science, Econlit, PsycINFO, CINAHL, EMBASE, and informit will be systematically searched from inception to date of search. Published peer-reviewed, English language articles reporting PROMs measuring QOL or SWB outcomes in children and adolescents with cerebral palsy will be included. One reviewer will conduct the initial search and screen titles and abstracts for potentially eligible studies. The search will be performed in November 2017. To reduce the likelihood of reviewer selection bias, two other reviewers will independently screen a randomly selected sub-sample (10%) of the citations. Two reviewers will then retrieve full texts of potentially eligible studies and assess them against predefined inclusion criteria. The suitability of selected PROMS for use in economic evaluations of young people with cerebral palsy will be assessed using the International Society of Quality of Life Research (ISOQOL) recommended Minimum Standards and the Patient-Centered Outcomes and Comparative Effectiveness Research (CREATE) checklist. A narrative synthesis of extracted data will be presented including study descriptive data, PROMs measurement properties, settings in which they were applied and the valuation methods. Recommendations for practice on the selection of PROMs for use in economic evaluations of children and adolescents with cerebral palsy will be presented.

Ethics and dissemination: Ethical approval is not required as the proposed systematic review will not use primary data. The results of this study will be widely disseminated through publication in a peer-reviewed journal and conference presentation(s).

Systematic review registration number: International Prospective Register of Systematic Reviews (PROSPERO) number CRD42016049746.

Strength and limitations of this study

- One of the strengths of this study is that an extensive literature search of existing PROMs (both preference-based and non-preference-based) that are used to assess QOL in children and young people with cerebral palsy will be performed.
- Another strength of the systematic review is that a comprehensive examination of the suitability of preference-based PROMs for use within both trial and model-based economic evaluations of paediatric populations with cerebral palsy will be performed.
- A limitation of this systematic review is the exclusion of studies that are not published in English, which may mean that some articles examining quality of life outcomes in young people with cerebral palsy in non-English speaking countries maybe omitted.

INTRODUCTION

Patient reported outcome measures (PROMs) are increasingly being used in health services research to inform healthcare resource allocation decisions. [1, 2] PROMs assess a patient's subjective assessment of their well-being, health status or quality of life (QOL) at a single point in time and are collected via standardized, self-report questionnaires. [3, 4] PROMs may be differentiated into condition-specific and generic measures. Condition-specific measures are designed to assess health outcomes in people with specific medical conditions (e.g., the cerebral palsy quality of life [CP-QOL] questionnaire); whilst generic measures (e.g., the Pediatric Quality of Life Inventory [PedsQL]) are applicable across all disease areas. Condition-specific and generic measures can be subdivided into preference/utility-based and non-preference-based PROMs. Non-preference-based measures use a simple summative scoring system whereby individual items or dimensions are used to generate summary scores. [5]Preference-based PROMs typically incorporate scoring algorithms which are premised on preferences of general population samples for health states generated through valuation methods such as the standard gamble (SG) and time trade-off (TTO) techniques, and are usually anchored between 0 (representing death) to 1 (representing optimal health). Preference-based PROMs enable the calculation of quality adjusted life years (QALYs) for use in cost-utility analysis, a type of economic evaluation.[5-7] QALYs are a routinely used standard measure of benefit in economic evaluation.[8]

Cerebral palsy is a complex chronic disorder of motor impairment that requires long-term medical and supportive care services. It is the leading cause of physical disability in childhood with prevalence rates ranging between 2.0 and 3.5 per 1000 live births worldwide. [9] There are broad variations in the definition and classification of cerebral palsy. However, the International Executive Committee for the Definition of cerebral palsy, recommend the following definition: "Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy, and by secondary musculoskeletal problems". [10] As such, cerebral palsy has ubiquitous impacts on all aspects of a child's life. Cerebral palsy has been shown to have a negative effect on the QOL of children with the condition. [11, 12] The cost of care for persons with cerebral palsy in Australia was estimated

at AUD$43,431 per person per year in 2007 with the total annual national economic cost of cerebral palsy estimated at AUD$1.47 billion (of which approximately 37% was borne by the individual and/or their family). [13] In the United States of America in 2005, the total Medicaid expenditures averaged $43,338 for a child with cerebral palsy [14] and the average lifetime cost of cerebral palsy (based on 2003 US dollars) was estimated to be $921,000 per person of which 81% are indirect costs and 19% are direct costs. [15] In 2007, a Dutch study on children with cerebral palsy, found the annual cost to be €40,265 per child.[16] Clearly, it is vital to consider the impact of the cost of long-term care on young people and /or their families. With these rising costs and competing healthcare demands, there is a growing need for optimal funding decisions. Economic evaluation is an important technique to help decision-makers determine the relative value for money of service innovations in health care and requires the robust measurement of appropriate health, health status, QOL or subjective well-being (SWB) outcomes [17]. This highlights the importance of finding appropriate PROMs for economic evaluation of services targeted at children and young people with this condition.

The World Health Organisation defines QOL as "an individual's perception of their position in life in the context of the culture and value system in which they live, and in relation to their goals, expectations, standards, and concern". [18] QOL is a broad concept which refers to the influence of all facets of an individual's life on their general well-being including HRQOL. HRQOL refers to an individual' self-perceived assessment of their health and its subsequent effect on their life and is defined as a subjective multi-dimensional construct of well-being and functioning based on physical, emotional, mental, social and behavioural features as perceived by patients. [19] In literature these two concepts, QOL and HRQOL are used interchangeably, [20] for the purposes of this systematic review both terms will be considered in the search strategy.

The main aim of this systematic review is to identify studies that have used PROMs to assess QOL and SWB in children with cerebral palsy and to evaluate the suitability of these PROMs for application in economic evaluations targeted at this population. Previous systematic reviews in cerebral palsy have focused on assessing performance of psychometric-based physical activity and/or participation measures [21, 22] and QOL [23-25]. These reviews did not distinguish between measures associated with different cerebral palsy health states depicting the levels of severity as classified using a number of metrics including gross motor

function [26] manual ability [27] and communication [28].” Further, only Janssens et al. [25] included preference-based outcome measures in their review even though the population was that of children and young people living with neurological disabilities and not exclusive to those with cerebral palsy. This current review may be distinguished from previous ones in three main ways:

Firstly, this review is focused exclusively on cerebral palsy. Secondly, the review will assess the appropriateness of the PROMs applied for informing QOL associated with different cerebral palsy health states for the purposes of model-based economic evaluation. Thirdly, information on the contexts in which the PROMs have been used will also be extracted and collated so as to determine the suitability of particular PROMs for particular settings (with context defined according to the functional ability of populations as measured by the Gross Motor Function Classification System (GMFCS) [26], in which the instruments have been used)

The specific objectives of the review are:

1. To identify PROMs that are used to measure QOL and SWB outcomes in children and young people aged 0-18 years with cerebral palsy
2. To establish the different contexts in which the PROMs have been applied
3. To critically examine the suitability of preference-based PROMs for use within economic evaluations targeted at this population

Review questions

The proposed review will seek to address the following specific research questions:

1. What preference-based and non-preference-based PROMs are used to measure QOL and SWB outcomes in children and young people with cerebral palsy?
2. How suitable are the identified PROMs for use within economic evaluations of paediatric populations with cerebral palsy and in what contexts?

METHODS

Design

The protocol has been registered with International Prospective Register of Systematic Reviews (PROSPERO) [registration number CRD42016049746] and it has been developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.[29] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. [30]

The systematic review will follow a structured two-stage approach. Firstly, all PROMS (both preference-based and non-preference-based) and articles/studies reporting details of development and/or application of PROMs used to measure QOL and/or SWB in young people with cerebral palsy will be identified. Second, each of the PROMS identified will be appraised using two checklists: The International Society of Quality of Life Research (ISOQOL) recommended Minimum Standards for Patient-Reported Outcome Measures,[31] and the Patient-Centered Outcomes and Comparative Effectiveness Research (CREATE) checklist for reporting valuation studies.[32] The ISOQOL was included for purposes of appraising non-preference-based and CREATE will be used to appraise the candidate utility-based (preference-based) PROMs. A University of South Australia Health Sciences Librarian with expertise in designing systematic reviews will be available to the team and will provide guidance on the search strategies for each database.

Eligibility criteria

Published, peer-reviewed, English-language articles reporting QOL and SWB outcomes of children and young people aged 0-18 years with a diagnosis of cerebral palsy will be eligible for inclusion in the initial stage of the systematic review.

There is currently no consensus regarding the inclusion or exclusion of non-English language articles to systematic reviews. Some authors seem to suggest that excluding non-English language studies from systematic reviews may lead to language-bias and subsequently lead to inaccurate conclusions. However, other studies have reported results contrary to this which suggest that restricting searches to the English language does not alter the outcome of systematic reviews and meta-analyses [33, 34]. This is more so true in clinical fields which have a high prevalence of English language articles and research.

Inclusion criteria:

- The review will include all study designs in the preliminary search because it is expected that the number of preference-based PROMs in this field is relatively small;

- There will be no restrictions in terms of setting for the initial search because the literature in this field is likely to be relatively small and any restrictions at this stage over and above 'care-related' (rather than generic) would hinder any wider recommendations;
- To allow for a relatively broader definition of carers beyond primary carers, studies where PROMs were completed by either, the child, parent (primary caregiver), clinician, teachers or school principal etc. will be included.
- Both preference and non-preference instruments will be included as well as generic and condition specific instruments.

Exclusion criteria:

- Studies focused only on adults. Studies that examine participants across both child/adolescent and adult age ranges will only be included if majority of the sample are children/adolescent and 0-18yrs and if results are for the two categories reported separately
- Studies where QOL and SWB data is on parents and caregivers of children with cerebral palsy;
- Publications that are not peer-reviewed including unpublished dissertations, reports, conference presentations, discussion papers and any grey literature. This is so as to ensure that only articles that have gone through the rigorous review and editorial process are included.

Search strategy

An extensive search of the literature search will be conducted in nine electronic bibliographic databases from database inception to the date of the search: MEDLINE (including in-process and other non- indexed citations viaOvid interface,); Scopus (via Elsevier interface); The Cochrane Library (including the Cochrane CENTRAL, EED and HTA); Web of Science Core Collection; Econlit (via Ovid interface); EMBASE (via Ovid interface; PsycINFO (via Ovid interface); CINAHL (via EBSCO-host); informit (via informit interface). The primary electronic search strategy was designed for MEDLINE and adapted as appropriate for each of the databases. The full search strategy is presented in the supplementary appendix. Key words and Medical Subject Headings (MeSH) terms include: "cerebral palsy", "children", "adolescents", "quality of life", "health related quality of life" and "well-being". To ensure that all significant literature is retrieved, both forward (inspecting articles in order to

determine if key articles have been cited) and backward (examining reference lists) citation checking will be performed on all full texts examined so as to ensure that no eligible studies are missed out. Results from the search and retrieved references will be imported and managed in Thomson Reuters™ Endnote version X7.1 (2014) reference management software. The search will be performed in November 2017.

Selection process

First, all titles and abstracts of articles resulting from the search will be screened against the eligibility criteria independently by the lead review author (CMK), as has been done elsewhere. [35-37] The primary aim of screening is to identify articles that meet the inclusion criteria. Full texts will be retrieved at this initial stage only if the abstract contains limited information about the study and duplicate articles will be removed. To reduce the possibility of selection bias, a randomly selected subset of citations (20%) will be independently assessed by two other members of the review team (GC and EH).[37] Cohen's Kappa statistic will be estimated to measure interrater reliability (degree of agreement) between the reviewers. [38-40] Cohen's Kappa statistic values less than or equal to 0 indicate no agreement, 0.01–0.20 (none to slight), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial), and 0.81–1.00 (strong) agreement. If the interrater reliability is less than 0.80, i.e., strong level of agreement, [39] an additional subset of articles (25%) will be will be independently assessed. If the degree of agreement between the review authors is still less than 0.80, then the rest of the articles will be independently screened. Differences will be resolved by discussion and consultation with the review team. Second, full texts of potential candidate studies will be obtained and assessed for inclusion in the review. To ensure that all relevant literature is retrieved, both forward (inspecting in order to determine if key articles have been cited) and backward (examining reference lists) citation chasing will be performed. Where necessary, study authors will be contacted for clarification and additional information to inform study selection. Each stage of the selection process will be outlined in a PRISMA-style flow chart and assessed against the 27 item PRISMA checklist.

Data collection

Summary data of each included PROM and article will be extracted into a data extraction form specifically designed for this review. Summary tables will be created in Microsoft Office Excel 2013 for (1) information about the candidate PROMs and (2) information

pertaining to the identified studies. The information to be extracted from the included studies will be the following:

1. Descriptive information about study: date of publication; country of origin; sample size; study type and setting; study population and characteristics (including age, gender and Gross Motor Functioning Classification System); study key results and conclusions.

2. Descriptive information about the measure: name of PROM; domains/dimensions; number of items; description of the items; response method; method of administration; interpretation and summary scoring.

3. Information about valuation of measure i.e. have preference weights been collected from a representative sample of children and adolescents with cerebral palsy? health states valued; preference elicitation method; population preference weights.

Two other reviewers will independently appraise the quality and suitability of the preference-based PROMs for measuring outcomes in paediatric populations with cerebral palsy. Any disagreements will be resolved by discussion and consultation with the review team. This evaluation will also follow ISOQOL checklist (for internal consistency reliability, test-retest reliability, content validity, construct validity, criterion validity, responsiveness, interpretability of scores, respondent burden and investigator burden) [31] and the CREATE checklist (for reporting valuation studies) to appraise the candidate utility-based PROMs. [32]

Data synthesis

A summary of included studies and PROMs will be presented in line with recommendations from the Cochrane Collaboration.[41] The main features of the included studies, instrument descriptions and contexts in which they are applied and information about valuation methods will be summarised into three tables.[42] Using this information, the suitability of each of the PROMs identified for use in economic evaluation will be assessed and comparisons and disparities between instruments will be described.

Discussion

To the best of our knowledge, this is the first systematic review that will comprehensively assess existing PROMs (both preference-based and non-preference-based) that are used to measure QOL in children and young people with cerebral palsy. Multiple bibliographic databases will be systematically searched from inception to date of search. This review will advance the field of health economics research in the following ways: First, the review will identify PROMs used to measure QOL and SWB in young people with cerebral palsy aged 0-18 years. Second, the review will establish the different contexts in which the PROMs have been applied. Third, the systematic review will provide evidence on the suitability of preference-based PROMs for use within both trial and model-based economic evaluations of paediatric populations with cerebral palsy.

A limitation of this systematic review is the exclusion of studies that are not published in English, which may mean that we miss some articles examining quality of life outcomes in young people with cerebral palsy in non-English speaking countries. However based on results of previous reviews [22, 24, 25] in this field as well as expertise and research experience of the research team, we do not anticipate a large number of non-English articles in this field and are therefore confident that no significant difference will be made by excluding them.

Ethics and dissemination

The main aim of this review is to provide a systematic review of existing published literature and as such ethical approval to conduct this research is not required. This systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016049746) [43], registration number CRD42016049746. The findings of this review will be disseminated as a peer-reviewed journal article and will be presented at both national and international conferences.

Contributions

JR, RR, GC and CMK formulated the idea for the study. CMK wrote the first draft and the co-authors (EH, GC, RR, JR) revised the protocol for important intellectual content. CMK will act as a guarantor for the work.

Acknowledgements

CMK is supported by the Australian Government Research Training Program Scholarship.

References

1. National Institute for Health and Care Excellence NICE. *Guide to the methods of technology appraisal 2013*. 2013.

2. Deshpande, P.R., et al., *Patient-reported outcomes: A new era in clinical research.* Perspect Clin Res, 2011. **2**(4): p. 137-44.

3. Acquadro, C., et al., *Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group meeting at the Food and Drug Administration, February 16, 2001.* Value Health, 2003. **6**(5): p. 522-31.

4. Willke, R.J., L.B. Burke, and P. Erickson, *Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels.* Control Clin Trials, 2004. **25**(6): p. 535-52.

5. Brazier, J., Ratcliffe, J. Salmon, J, A. and A. Tsuchiya, *Measuring and Valuing Health Benefits for Economic Evaluation*. 2017, London: Oxford University Press.

6. Drummond MF, S.M., Torrance GW, O'Brien BJ, Stoddart GL. , *Methods for the Economic Evaluation of Health Care Programmes*. 2005, Oxford: Oxford University Press.

7. Neumann, P.J., S.J. Goldie, and M.C. Weinstein, *Preference-Based Measures in Economic Evaluation in Health Care.* Annual Review of Public Health, 2000. **21**(1 1): p. 587-611.

8. Brazier, J.E., S. Dixon, and J. Ratcliffe, *The role of patient preferences in cost-effectiveness analysis: a conflict of values?* Pharmacoeconomics, 2009. **27**(9): p. 705-12.

9. Colver, A., C. Fairhurst, and P.O. Pharoah, *Cerebral palsy.* Lancet, 2014. **383**(9924): p. 1240-9.

10. Rosenbaum, P., et al., *A report: the definition and classification of cerebral palsy April 2006.* Dev Med Child Neurol Suppl, 2007. **109**: p. 8-14.

11. Russo, R.N., et al., *Self-esteem, self-concept, and quality of life in children with hemiplegic cerebral palsy.* J Pediatr, 2008. **153**(4): p. 473-7.

12. Livingston, M.H., et al., *Quality of life among adolescents with cerebral palsy: what does the literature tell us?* Dev Med Child Neurol, 2007. **49**(3): p. 225-31.

13. Access Economics, *The Economic Impact of Cerebral Palsy in Australia in 2007, Report for CP Australia*. 2008, Access Economics: Canberra, Australia.

14. Kancherla, V., et al., *Medical expenditures attributable to cerebral palsy and intellectual disability among Medicaid-enrolled children.* Res Dev Disabil, 2012. **33**(3): p. 832-40.

15. Centers for Disease Control and Prevention., *Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment--United States, 2003.* MMWR Morb Mortal Wkly Rep, 2004. **53**(3): p. 57-9.

16. Hoving, M.A., et al., *Intractable spastic cerebral palsy in children: a Dutch cost of illness study.* Dev Med Child Neurol, 2007. **49**(5): p. 397-8.

17. Brazier J, et al., *Measuring and Valuing Health Benefits for Economic Evaluation.* 2007, London: Oxford University Press.

18. *The World Health Organization quality of life assessment (WHOQOL): Position paper from the World Health Organization.* Social Science & Medicine, 1995. **41**(10): p. 1403-1409.

19. Ravens-Sieberer, U., et al., *Generic health-related quality-of-life assessment in children and adolescents: methodological considerations.* Pharmacoeconomics, 2006. **24**(12): p. 1199-220.

20. Karimi, M. and J. Brazier, *Health, Health-Related Quality of Life, and Quality of Life: What is the Difference?* Pharmacoeconomics, 2016. **34**(7): p. 645-649.

21. Harvey, A., et al., *A systematic review of measures of activity limitation for children with cerebral palsy.* Dev Med Child Neurol, 2008. **50**(3): p. 190-8.

22. Morris, C., J.J. Kurinczuk, and R. Fitzpatrick, *Child or family assessed measures of activity performance and participation for children with cerebral palsy: a structured review.* Child Care Health Dev, 2005. **31**(4): p. 397-407.

23. Davis, E., et al., *Paediatric quality of life instruments: a review of the impact of the conceptual framework on outcomes.* Dev Med Child Neurol, 2006. **48**(4): p. 311-8.

24. Carlon, S., et al., *A systematic review of the psychometric properties of Quality of Life measures for school aged children with cerebral palsy.* BMC Pediatr, 2010. **10**: p. 81.

25. Janssens, A., et al., *Measurement properties of multidimensional patient-reported outcome measures in neurodisability: a systematic review of evaluation studies.* Dev Med Child Neurol, 2016. **58**(5): p. 437-51.

26. Palisano, R., et al., *Development and reliability of a system to classify gross motor function in children with cerebral palsy.* Dev Med Child Neurol, 1997. **39**(4): p. 214-23.

27. Eliasson, A.C., et al., *The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability.* Dev Med Child Neurol, 2006. **48**(7): p. 549-54.

28. Hidecker, M.J., et al., *Developing and validating the Communication Function Classification System for individuals with cerebral palsy.* Dev Med Child Neurol, 2011. **53**(8): p. 704-10.

29. Shamseer, L., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration & explanation.* BMJ, 2015. **349**.

30. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* PLoS Med, 2009. **6**.

31. Reeve, B.B., et al., *ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research.* Qual Life Res, 2013. **22**(8): p. 1889-905.

32. Xie, F., et al., *A Checklist for Reporting Valuation Studies of Multi-Attribute Utility-Based Instruments (CREATE).* Pharmacoeconomics, 2015. **33**(8): p. 867-77.

33. Morrison, A., et al., *The effect of English-Language restriction on systematic review-based meta-analyses: A systematic review of emipirical studies.* International Journal of Technology Assessment in Health Care, 2012. **28**(2): p. 138-144.

34. Moher, D., et al., *The inclusion of reports of randomised trials published in languages other than English in systematic reviews.* Health Technol Assess, 2003. **7**(41): p. 1-90.

35. Bhattarai, N., et al., *Economic evaluations on centralisation of specialised healthcare services: a systematic review of methods.* BMJ Open, 2016. **6**(5).

36. Kigozi, J., et al., *Estimating productivity costs using the friction cost approach in practice: a systematic review.* The European Journal of Health Economics, 2016. **17**(1): p. 31-44.

37. Mccaffrey, N., et al., *Protocol for a systematic review of preference-based instruments for measuring care-related outcomes and their suitability for the palliative care setting.* BMJ open, 2016. **6**(9): p. e012181.

38. Cohen, J., *A Coefficient of Agreement for Nominal Scales.* Educational and Psychological Measurement, 1960. **20**(1): p. 37-46.

39. Orwin., E.G., *Evaluating coding decisions*, in *The Handbook of Research Synthesis*, L.H. Cooper H, Editor. 1994, Russell Sage Foundation: New York.

40. McHugh, M.L., *Interrater reliability: the kappa statistic.* Biochemia Medica, 2012. **22**(3): p. 276-282.

41. Ryan R. *'Cochrane Consumers and Communication Group: meta-analysis*. December 2016. DOI: http://cccrg.cochrane.org.

42. Green, B.N., C.D. Johnson, and A. Adams, *Writing narrative literature reviews for peer-reviewed journals: secrets of the trade.* Journal of Chiropractic Medicine, 2006. **5**(3): p. 101-117.

43. Mpundu-Kaambwa, C.H., E.; Chen, G.; Russo, R.; Ratcliffe, J. *A systematic review of quality of life outcome measures for children with cerebral palsy*. PROSPERO International prospective register of systematic reviews, 2016.

Appendix I: MEDLINE search strategy

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present. Includes subsets: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily

#	Searches
1	Cerebral Palsy/
2	(Cerebral pals* or CP or spastic diplegia* or little disease or little's disease or hemiplegia or quadriplegia).tw,kw .
3	1 or 2
4	adolescent/ or child/
5	(Child* or adolescen* or teen* or pediatric* or paediatric* or youth or young * toddler or infant).tw,kw.
6	4 or 5
7	"Quality of Life"/ or quality-adjusted life years/
8	("quality of life" or QoL or HRQoL or HRQL or HRQOL or QL or health related QOL or hql or hqol or h-qol or hr-qol or quality adjusted life or qaly* or qald* or qale* or qtime* or disability adjusted life or daly* or health utilit* or health outcomes or patient outcome or functioning or activit* or participation or health status or functional status).tw,kw .
9	(Quality adj2 (well-being or wellbeing)).tw,kw.
10	qwb.tw,kw.
11	or/7-10
12	3 and 6 and 11
13	"surveys and questionnaires"/ or self-report/
14	(Instrument* or tool* or measure* or test* or dimension* or multidimension* or scale* or rating* or item response or properties or domain* or psychometric* or modified or schedule* or evaluat* or classification* or inventor* or index or indice* or scale* or question* or form or valid* reliab* assess* repeatability or acceptability or responsiveness or feasibility or PROM or child report or self-assess* or preference-based instrument or multi-attribute utility cost utility).tw,kw .
15	13 or 14
16	12 and 15
17	limit 16 to English language

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	1
Sponsor	5b	Provide name for the review funder and/or sponsor	1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	1
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8,14

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.