

CPQOL

Cerebral Palsy Quality of Life

-Manual

Version 2 July 2013

Quality of Life Questionnaire
for Children (CP QOL-Child)



Cerebral Palsy Quality of Life Manual (CP QOL-Child)

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Preface

This manual describes the development of the Cerebral Palsy Quality of Life Questionnaire for Children (CP QOL–Child), a condition-specific quality of life (QOL) questionnaire for children with cerebral palsy aged 4 to 12 years. CP QOL-Child was developed by an international multidisciplinary team of clinical and child health researchers, in collaboration with parents, and children with cerebral palsy. The team spanned Australia, the United States, Germany, and Scotland.

The CP QOL-Child was developed in response to an international call for a new QOL instrument for children with cerebral palsy. In 1991, the United Cerebral Palsy Association (UCPA) adopted its mission statement: ‘To affect positively the quality of life of persons with cerebral palsy’. QOL assessment is now a mandatory component of clinical trial research (1).

The CP QOL–Child is a measure of quality of life for children with cerebral palsy that can be used by researchers, clinicians, health professionals and educators to measure and assess changes in children’s QOL. This manual provides only basic information about administering and scoring the CP QOL-Child. Readers interested in background literature, development of the CP QOL-Child and psychometric properties should refer to academic publications.

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Section 1: The Cerebral Palsy QOL Questionnaire for Children (CP QOL-Child)

What is the CP QOL Child?

The Children with Cerebral Palsy Quality of Life Questionnaire (CP QOL-Child) is a measure of quality of life for children with cerebral palsy. It has been developed specifically for children with cerebral palsy. The CP QOL-Child was developed in consultation with parents, children and health professionals. Further information about the background literature, development and results are provided in academic publications (refer to Appendix 1).

Who is the CP QOL Child designed for?

The CP QOL-Child was developed and tested for use with children with cerebral palsy. It is designed for children aged 4-12 years. There are two versions of the CP QOL-Child:

1. Parent-proxy version (for parents of children aged 4-12 years), comprising 65 items;
2. Child self-report version (for children aged 9-12 years), comprising 53 items.

Parents and children may report different levels of QOL. Consequently, it is recommended that both versions are used, if possible. Statistical analyses should be conducted on both parent proxy and child self-report scores and both should be reported and interpreted.

What does the CP QOL- Child measure?

The CP QOL-Child measures the following seven areas of a child's life:

- Social wellbeing and acceptance
- Participation and physical health
- Feelings about functioning
- Emotional wellbeing and self-esteem
- Pain and impact of disability
- Access to services*
- Family health*

*Access to services, and Family health are only included in the parent proxy version of the questionnaire.

When can the CP QOL-Child be used?

The CP QOL Child can be used by researchers, clinicians, health professionals and educators for a variety of purposes, including: conducting research to determine whether an intervention has increased a child's QOL; and as an assessment to gain insight into several aspects of children's lives.

Section 2: Administering the CP QOL-Child

Consenting to Complete the CP QOL-Child

The parent proxy version of the CP QOL-Child is suitable for parents of children with cerebral palsy aged 4-12 years. The child self-report version of the CP QOL-Child is suitable for children with cerebral palsy aged 9-12 years. The user should consider and obtain the necessary consent.

It is important to assess whether a child has the intellectual ability to complete the child self-report questionnaire. To determine whether a child can complete the questionnaire, it is useful to ask the child's parents or guardians. It is important to explain to the parent or guardian what type of questions would be asked of the child and how the child would need to record their responses. The child does not need to physically fill out the questionnaire. However they do need the ability to understand the questions and choose an answer.

The CP QOL-Child has been tested using two methods of administration:

1. Face to face interview;
2. Mailout questionnaire.

Either method can be used. Instructions for each method follow.

Face to face Interview

For either parent proxy or child self-report, it is important that you read out the instructions on the first page of the questionnaire.

Parent Proxy Report

‘We want to ask you some questions about how you think your child FEELS about aspects of their life such as family, friends, health and school. Each question begins with “How do you think your child FEELS about.....?” It is important for you to report how you believe your child feels. Sometimes it is difficult to know how your child is feeling. Please just try and answer as best as you can. For each question we want you to circle the best number that shows how you think your child FEELS. You can circle any number from 1 (Very unhappy) to 9 (Very happy). This questionnaire is measuring how your child feels, not what they can do.’

Child Self-Report

‘We want to ask you some questions about your life such as your family, your friends, your health and your school. Each question begins with “How do you FEEL about.....?” For each question we want you to circle the best number that shows how you FEEL. You can circle any number from 1 (Very unhappy) to 9 (Very happy). This questionnaire is measuring how you feel, not what you can do.’

If either a child or a parent asks the meaning of a question, the interviewer should ask the parent or child to complete the questionnaire based on what they think the question means. If a parent or child refuses to complete the CP QOL-Child or starts to complete it and doesn’t want to finish it, they do not need to complete it; completion is voluntary.

Mailout questionnaire

If the CP QOL-Child is to be used in a mail survey, the researchers should ensure they have discussed the questionnaire with the parent, either in person or on the telephone. This is particularly important in order to determine whether the child can complete the child self-report questionnaire.

Data Entry, Cleaning and Scoring

Information on data entry, data cleaning and scoring is provided in Appendix 2.

Section 3: Contact Information

If you would like further information on the CP QOL-Child, please visit the CP QOL website at

www.cpqol.org.au

Alternatively, contact:

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Appendix 1: Publications on CPQOL-Child

1. Davis E; Mackinnon A; Davern M; Boyd R; Bohanna I; Waters E; H.K Graham; Reid S; Reddihough D. Description and psychometric properties of the CP QOL-Teen: a quality of life questionnaire for adolescents with cerebral palsy. *Research in Developmental Disabilities* 2013; 34: 344-35
2. Davis E, Mackinnon A, Waters E. Parent-proxy reported quality of life for children with cerebral palsy: Is it related to parental psychosocial distress? *Child: Care, Health and Development*. (Published online 15th June 2011) <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2214.2011.01267.x/full>
3. Davis E, Shelly A, Waters E, Davern M: Measuring the quality of life of children with cerebral palsy: comparing the conceptual differences and psychometric properties of three instruments. *Dev Med Child Neurol*; 2010 Feb;52(2):174-80
4. Waters E, Davis E, Ronen G, Rosenbaum P, Livingston M, Saigal S. Quality of life instruments for children and adolescents with neurodisabilities: how to choose the appropriate instrument. *Developmental Medicine and Child Neurology* 2009; 51(8), 660-669.
5. Davis E, Davies B, Wolfe R, Raadsveld R, Heine B, Thomason P, Dobson F, Graham K. A randomized controlled trial of the impact of therapeutic horse riding on the quality of life, health, and function of children with cerebral palsy. *Developmental Medicine and Child Neurology* 2009; 51: 111-119.
6. Davis E, Shelly A, Waters E, Reddihough D, Boyd R, Cook K, Casey E. The impact of caring for a child with cerebral palsy: Quality of life for mothers and fathers. Submitted to *Child: Care, Health and Development*, 2009; 36(1),63-73.
7. Davis E, Shelly A, Waters E, Mackinnon A, Reddihough D, Boyd R, Graham HK. Quality of life for adolescents with cerebral palsy: Perspectives of adolescents and parents. *Developmental Medicine and Child Neurology* 2009; 51: 193–199.
8. Waters E, Shelly A, Davis E. Condition-specific instruments to measure the Quality of Life (QOL) of Children and Adolescents with Cerebral Palsy (CP). Submitted to *Jenkinson, Harris and Williams: Quality of Life Measurement in Neurodegenerative Disorders*, in press.
9. Davis E, Waters E. Children with cerebral palsy, psychometric analysis and quality of life. In: Victor A Preedy, editor. *Handbook of Disease Burdens and Quality of Life Measures*. New York: Springer; 2008.
10. Shelly A, Davis E, Waters E, Mackinnon A, Reddihough D, Boyd R, Reid S, Graham HK. The Relationship Between Quality of Life (QOL) and Functioning for Children with Cerebral Palsy. Does Poor Functioning equate with Poor QOL? *Developmental Medicine and Child Neurology* 2008; 50:199-203.
11. Davis E, Waters E, Mackinnon A, Reddihough D, Boyd R, Graham K. Correspondence: Quality of Life of Children with Cerebral Palsy: Importance of condition-specific instrument and proxy reports. *Developmental Medicine and Child Neurology* 2008; 50: 167.

Appendix 1: Publications on CPQOL-Child

12. Davis E, Waters E, Shelly A and Gold L. Children and Adolescents, Measuring the Quality of Life of. In: Kris Heggenhougen and Stella Quah, (eds) International Encyclopedia of Public Health, Vol 1. San Diego: Academic Press; 2008. pp. 641-648.
13. Davis E, Nicolas C, Waters E, Cook K, Gibbs L, Gosch A, Ravens-Sieberer U. Parent proxy and child self-reported health related quality of life: Using cognitive methods to explain the discordance. *Quality of Life Research* 2007; 16: 863-871.
14. Waters, E, Davis, E, Mackinnon, A., Boyd, R, Graham, H.K, Lo, S.K, Wolfe, R., Stevenson, R., Bjornson, K., Blair, E, Hoare, P, Ravens-Sieberer, U, Reddihough, D. Psychometric properties of the quality of life questionnaire for children with CP. *Developmental Medicine and Child Neurology*, 2007; 49: 49-55.
15. Davis E & Waters E. Social exclusion in children with cerebral palsy. Book Chapter. In K. Cook & K. Gilbert (eds). *Life on the margins: Implications for health research*. Frenchs Forest: Pearson Education Australia. pp181-189, 2006.
16. Davis E, Waters E, Boyd R, Reddihough D, McKinnon A, Graham K & Mehmet Radji O. Paediatric QOL Instruments: review of the impact of the conceptual framework on outcomes. *Developmental Medicine and Child Neurology* 2006; 48: 311-318.
17. Waters E, Maher E, Salmon L, Reddihough D, Boyd R. Developing a new quality of life scale for children with cerebral palsy. *Child: Care, Health and Development*, 2005; 31:127-135.
18. Davis E, Waters E, Boyd R, Reddihough D, McKinnon A, Graham K & Mehmet Radji O. Paediatric QOL Instruments: Critical concerns and setting a research agenda. *Developmental Medicine and Paediatric Neurology* 2006; 48:311-318.
19. Waters, E, Davis, E., Lo, SK., Boyd, R, Reddihough, D., Graham HK, Mackinnon, A., Wolfe, R., Stevenson, R., Bjornson, K., Blair, E., Hoare, P., Ravens-Sieberer, U. (2007). Cerebral Palsy Quality of Life Questionnaire for Children (CP QOL-Child): Psychometric Properties of Parent Proxy Questionnaire. Submitted to *Developmental Medicine and Child Neurology*, 49, 49-55.
20. Waters E, Davis E, Reddihough D, Graham HK, Mackinnon A, Wolfe R, Stevenson R, Bjornson K, Blair E, Hoare P, Ravens-Sieberer U & Boyd R. A new condition-specific quality of life scale for children with cerebral palsy. *Patient Reported Outcomes Newsletter*, 2005; 35:10-1.
21. Davis, E, Waters E & Mehmet-Radji O. Re: A structured review of studies on health-related quality of life and economic evaluation in pediatric acute lymphoblastic leukemia. *Journal of the National Cancer Institute* 2005; 97: 1-2.
22. Waters, E & Maher, E. 2004. Quality of Life. In V. Moyer (Eds.), *Evidence-based Pediatrics & Child Health*. British Medical Journal Books.

Appendix 2: Data Entry, Cleaning & Scoring

Data Entry

The CP QOL-Child data should be entered into the statistical database in the order in which it appears on the questionnaire. The first question should be labelled qol1, the second question should be labelled qol2, and so on. The parent questionnaire finishes at qol65. The child questionnaire finishes at qol53. The parent and child data can be entered in the same columns as the parent and child questions are the same (that is, qol1 is the same for parents and for children).

Data Cleaning

Prior to scoring, it is important to check the range of values for each of the items against the expected or possible response values, and then clean the dataset. Cleaning will involve:

- Randomly checking for the accuracy of data entry (that is, every 10th questionnaire should be checked)
- Correcting any values of individual items which are found to be outside the appropriate range of expected values
- Implementing standardised systems for coding (for example, where a respondent has marked two response choices, the higher or lower value is chosen each time as the 'correct' response).

Appendix 2: Data Entry, Cleaning & Scoring

Scoring the CP QOL- Child

Scoring involves two steps:

- 1. Items are transformed to a scale with a possible range of 0-100;**
- 2. The algebraic mean of item values is computer for each domain.**

1. Items are transformed to a scale with a possible range of 0-100.

All other items can be recoded using the following formula:

If person scored 1, recode to 0
 If person scored 2, recode to 12.5
 If person scored 3, recode to 25
 If person scored 4, recode to 37.5
 If person scored 5, recode to 50
 If person scored 6, recode to 62.5
 If person scored 7, recode to 75
 If person scored 8, recode to 87.5
 If person scored 9, recode to 100

One item is not rated on a 9 point scale.

- Does your child worry about who will take care of them in the future? (Parent proxy);
- Do you worry about who will take care of you in the future? (Child self-report).

For this item the following formula must be used:

If person scored 1, recode to 0
 If person scored 2, recode to 25
 If person scored 3, recode to 50
 If person scored 4, recode to 75
 If person scored 5, recode to 100

Appendix 2: Data Entry, Cleaning & Scoring

2. Calculating mean scale scores

Table 1 contains the items that are included in each domain for the Parent proxy questionnaire.

Table 2 contains the items that are included in each domain for the child self-report questionnaire.

Table 1: Domains and Items for the Parent Proxy version of the CP QOL-Child

* Indicates items that begin with ‘How do you think your child feels about...’

Indicates items with many missing values in our study testing the psychometric properties and so were excluded from the analyses.

Domains	Items
Social wellbeing and acceptance	the way they get along with people, generally?* the way they get along with other children at preschool or school?* the way they get along with other children outside of preschool or school?* the way they get along with adults?* the way they get along with their teachers and/or carers?* going out on trips with the family?* the way they get along with their brothers and sisters?*# how they are accepted by their family?* how they are accepted by other children at preschool or school?* how they are accepted by other children outside of preschool or school?* how they are accepted by adults?* how they are accepted by people in general?*
Feelings about functioning	their ability to play on their own?* the way they communicate with people they know well?* the way they communicate with people they don’t know well?* the way other people communicate with them?* how they sleep?* the way they use their arms?* the way they use their hands?* their ability to keep up academically with their peers?* their opportunities in life?* their ability to dress themselves?* their ability to eat or drink independently?* their ability to use the toilet by themselves?*

Table 1 cont.

Domains	Items
Participation and physical health	their ability to play with friends?* their ability to participate at preschool or school?* their ability to participate in recreational activities?* their ability to participate in sporting activities?* their ability to participate in social events outside of preschool or school?* their ability to participate in their community?* their physical health?* the way they get around?* the way they use their legs?* being able to do the things they want to do?* their ability to keep up physically with their peers?*
Emotional wellbeing and self esteem	the way they get along with you?* the way they look?* their life in general?* themselves?* their future?* How happy is your child?
Access to Services	your child's access to treatment?* your child's access to therapy?* your child's access to specialised medical or surgical care?* your ability to get advice from a paediatrician?* your child's access to extra help with learning at preschool or school?* the special equipment they have at home?*# the special equipment they have at their school?*# the special equipment that is available in the community?*# your access to respite care?*# the amount of respite care you receive?*# how easy it is to get respite?*# your child's access to community services and facilities?*#

Table 1 cont.

Domains	Items
Pain and impact of disability	<p>Is your child bothered by hospital visits?</p> <p>Is your child bothered when they miss school for health reasons?</p> <p>Is your child bothered by being handled by other people?</p> <p>Does your child worry about who will take care of them in the future?</p> <p>Is your child concerned about having cerebral palsy?</p> <p>How much pain does your child have?</p> <p>How does your child feel about the amount of pain they have?</p> <p>How much discomfort does your child experience?</p>
Family Health	<p>your physical health?</p> <p>your work situation?</p> <p>your family's financial situation?</p> <p>how happy are you?</p>

Table 2: Domains and Items for the Child Self-Report version of the CP QOL-Child

* Indicates items that begin with 'How do you think your child feels about...'

Indicates items with many missing values in our study testing the psychometric properties and so were excluded from the analyses.

Domains	Items
Social wellbeing and acceptance	the way you get along with people, generally?* the way you get along with other children at preschool or school?* the way you get along with other children outside of preschool or school?* the way you get along with adults?* the way you get along with their teachers and/or carers?* going out on trips with your family?* the way you get along with their brothers and sisters?*# how you are accepted by your family?* how you are accepted by other children at school?* how you are accepted by other children outside of school?* how you are accepted by adults?* how you are accepted by people in general?*
Feelings about functioning	your ability to play on their own?* the way you communicate with people you know well?* the way you communicate with people you don't know well?* the way other people communicate with you?* how you sleep?* the way you use your arms?* the way you use your hands?* your ability to keep up academically with your peers?* your opportunities in life?* your ability to dress yourself?* your ability to eat or drink independently?* your ability to use the toilet by yourself?*

Table 2 cont.

Domains	Items
Participation and physical health	your ability to play with friends?* your ability to participate at preschool or school?* your ability to participate in recreational activities?* your ability to participate in sporting activities?* your ability to participate in social events outside of school?* your ability to participate in your community?* your physical health?* the way you get around?* the way you use your legs?* being able to do the things you want to do?* your ability to keep up physically with your peers?*
Emotional wellbeing and self esteem	the way you get along with your parents?* the way you look?* your life in general?* yourself?* your future?* How happy are you?
Pain and impact of disability	Are you bothered by hospital visits? Are you bothered when you miss school for health reasons? Are you bothered by being handled by other people? Do you worry about who will take care of you in the future? Are you concerned about having cerebral palsy? How much pain do you have? How do you feel about the amount of pain you have? How much discomfort do you experience?

References

1. Fayers PM, Hopwood P, Harvey A, Girling D, Machin D, Stephens R. Quality of life assessment in clinical trials-Guidelines and a checklist for protocol writers: The U.K. Medical Research Council Experience. *Eur J Cancer* 1997;33:20-28.
2. Streiner DL, Norman GR. *Health Measure Scales: a practical guide to their use*. New York: Oxford University Press; 1995.
3. Nunnally JC. *Psychometric Theory*. 2 ed. New York: Basic Books; 1978.
4. Carmines E, Zeller R. *Reliability and validity assessment*. Newbury Park: Sage Publications.; 1979.
5. Dite GS, Reddihough DS, Robert L. *Second Report of the Victorian Cerebral Palsy Register*. Melbourne: Department of Child Development and Rehabilitation, Royal Children's Hospital; 1995 1995.
6. Ravens-Sieberer U, KIDSCREEN team. KIDSCREEN. In: www.kidscreen.org; 2004.
7. Landgraf JM, Abetz L, Ware JA. *The CHQ User's manual*. First edition. Boston: The Health Institute, New England Medical Centre; 1996.
8. Waters E, Salmon L, Wake M. The Child Health Questionnaire in Australia: reliability, validity and population means. *Australian and New Zealand Journal of Public Health* 2000;24(2):207-210.
9. Wake M, Salmon L, Reddihough D. Health status of Australian children with mild to severe cerebral palsy: cross-sectional survey using the Child Health Questionnaire. *Developmental Medicine and Child Neurology* 2003;45:194-199.
10. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental Medicine and Child Neurology* 1997;39:214-223.
11. Morris C, Galuppi BE, Rosenbaum P. Reliability of family report for the Gross Motor Function Classification System. *Developmental Medicine and Child Neurology* 2004;46:455-460.