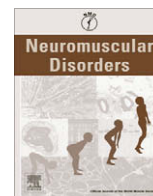




Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

Reliability of telephone administration of the PedsQL™ Generic Quality of Life Inventory™ and Neuromuscular Module™ in spinal muscular atrophy (SMA)☆

Sally Dunaway^a, Jacqueline Montes^a, Megan Montgomery^a, Vanessa Battista^a, Benjamin Koo^a, Jonathan Marra^a, Darryl C. De Vivo^a, Linda S. Hynan^b, Susan T. Iannaccone^c, Petra Kaufmann^{a,*}

^a SMA Clinical Research Center, Columbia University Medical Center, New York, NY, USA

^b Departments of Clinical Sciences (Biostatistics) and Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA

^c Departments of Pediatrics and Neurology, UT Southwestern Medical Center, Dallas, TX, USA

ARTICLE INFO

Article history:

Received 27 July 2009

Received in revised form 6 November 2009

Accepted 30 November 2009

Keywords:

Spinal muscular atrophy

Pediatric Quality of Life Inventory

Outcome measure

Telephone reliability

ABSTRACT

Clinical research visits are challenging for people with SMA because of limited mobility and intermittent illnesses. Missing data threaten the validity of research results. Obtaining outcomes remotely would represent a solution. To evaluate reliability of telephone administration of the PedsQL™ Pediatric Generic Core Quality of Life Inventory™ 4.0 (Generic) and Neuromuscular Module™ 3.0 (NM) in SMA, we recruited 21 participants of a Natural History Study for telephone administration of both modules no more than 7 days before or after an in-person study visit. We found excellent reliability between telephone and in-person administration of both modules with the NM slightly better than the Generic. Reliability of the child and parent forms was similar. We concluded that both modules can be administered reliably over the telephone to SMA patients and caregivers, expanding the utility of these tools in clinical trials. Notably, telephone administration is reliable in children as young as 8 years.

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1. Introduction

SMA is one of the most devastating neurological diseases of childhood. The disease affects an estimated 10–16 out of 100,000 infants, and children suffer from progressive muscle weakness caused by degeneration of lower motor neurons in the spinal cord and brainstem [1]. There is no known cure for SMA. However, potential therapies are being considered and the feasibility of conducting clinical trials in this population is increasingly documented [2].

For clinical trials in children with SMA, reliable and valid primary and secondary outcome measures are essential [3]. Quality of life evaluation during a clinical trial is important as it may help to determine if changes in clinical measurements have a meaningful impact on a patient's life. Health-related quality of life measurements that are specific and sensitive to the factors unique to a particular disease have become increasingly recognized as important outcome measures in clinical trials involving children with neuromuscular disorders [4–7]. Both generic and disease-specific measures have emerged that have the ability to capture patients' perceptions of the impact of an illness and the effect of the inter-

vention on their functioning and sense of well being. These measures allow the evaluators to gain a more comprehensive overview of the patient's health-related quality of life [8–10].

The PedsQL™ Pediatric Generic Core Quality of Life Inventory™ 4.0 (Generic) is a proprietary test measuring quality of life in children. This instrument is designed to enable comparisons across patient and healthy populations [11,12]. It is a validated measure for use with healthy school and community populations, as well as with pediatric populations with acute and chronic health conditions. The validity of the Generic module was demonstrated through comparisons of known groups, and correlations with other measures of disease burden. This instrument, which includes age specific questionnaires for children and parents, takes approximately 5 min to complete [12].

A separate Neuromuscular Module™ 3.0 (NM) was designed to assess patient's perception of disease relevant tasks and complements the generic core scales. It is a disease-specific questionnaire intended to evaluate the patient's perception of the neuromuscular disease state. Recent data supports the feasibility, reliability and validity of the PedsQL™ Generic and NM modules in pediatric patients with SMA [13].

Participation in clinical trials often requires frequent in-office visits, allowing a greater chance of missed visits and incomplete data collection due to these taxing demands on the patient. Clinical trials in the pediatric SMA population are challenging for several reasons. Most SMA patients are fragile and frequently suffer from respiratory infections making it difficult for them to attend sched-

☆ This work was done while Dr. Kaufmann was at Columbia University and does not relate to NINDS/NIH.

* Corresponding author. Address: 180 Fort Washington Ave., 5th Floor New York, NY 10032, USA. Tel.: +1 212 305 1326; fax: +1 212 305 9263.

E-mail address: pk88@columbia.edu (P. Kaufmann).

uled clinic or research visits [3,14]. Also, the limitations in mobility can make in-person clinic visits difficult. Past attempts at clinical research in SMA, and particularly in SMA Type I, have been associated with slow recruitment, a high rate of missed visits and study withdrawals [15].

In SMA, both the Generic module and the NM module have been shown to be reliable [4,5]. However, reliability of telephone administration of the PedsQL™ has not been assessed in SMA. A recent study concluded that children had similar interpretation of the items on the Generic module regardless of mode of administration [16]. The aim of this study is to compare the reliability of telephone administration of the PedsQL™ Generic and the NM module in SMA to the in-person administration. Establishing telephone reliability would allow us to gather quality of life data remotely, so that we can gather information during home based studies and when in-person visits are missed.

2. Participants and methods

2.1. Subjects

We included in this telephone reliability study consecutive SMA patients participating in a Natural History Study from the SMA Clinical Research Center at Columbia University Medical Center. Informed consent was obtained prior to enrollment and the IRB at Columbia University approved the study. Inclusion criteria consisted of participants aged 2–18 years with a diagnosis of SMA type I, II or III.

2.2. Procedures

Consecutive participants in the SMA Natural History Study were invited to participate and initially were randomly assigned to 1 of 2 groups. Group 1 had the Generic and NM module administered over the telephone no more than 1–7 days before an upcoming in-person study visit. The same questionnaires were administered during the in-person visit. Group 2 had the Generic and NM module interview in-person followed by telephone administration of the same questionnaires no more than 1–7 days after the in-person study visit. If a participant randomized to group 1 could not be reached by phone prior to coming in we scheduled a subsequent call at the time of their in-person visit. As a result, a number of participants randomized to an initial telephone interview ended up having an initial in-person interview. To correct for the resulting unequal group sizes, we used unbalanced randomization in the latter part of the study.

The Generic and NM modules were administered in-person according to published guidelines. The parent/child first completed the Generic module before completing the NM module. These paper-and-pencil questionnaires were self-administered for parents and for children ages 5–18 years after introductory instructions from the administrator. For children 2–4 years, only the parents answered the questionnaires. One experienced, trained interviewer administered the questionnaire and recorded the results when a child was unable to self-administer the modules because of a physical or cognitive impairment, and for all telephone interviews. Parents and children completed the instruments separately. The same questionnaires were administered to the same caregiver during the telephone interview.

During telephone administration, the Generic and NM modules parent proxy-reports were administered for all subjects aged 2–18 years. The child self-reports were administered in subjects 8–18 years old. Telephone administration involved reading the instructions, questions and all possible responses verbatim. The PedsQL™ was completed in English by both children and their par-

ents, with a translator available for patients and parents for whom English was not their primary language.

We used three raters and established reliability of telephone scoring by standardizing the way the questionnaire was given and by scoring simultaneously in 8 of the 20 participants.

2.3. Measures

The PedsQL™ Generic Core 4.0 module is a 23-item scale that covers four subscales: physical (eight items), emotional (five items), social (five items) and school functioning (five items). The scale consists of developmentally appropriate forms for children ages 2–4, 5–7, 8–12, and 13–18 years. Pediatric self-report is measured in children and adolescents ages 5–18 years, and parent proxy-report of child health-related quality of life is measured for children and adolescents ages 2–18 years. The instructions ask how much of a problem each item has been during the past 1 month. A five-point Likert response scale is utilized (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items are reverse-scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicated better health-related quality of life. Scale scores are computed as the sum of the items divided by the number of items answered [12].

The PedsQL™ NM module is a 25-item scale that encompasses three subscales: About My/My Child's Neuromuscular Disease (seventeen items), Communication (three items), and About Our Family Resources (five items). The format, instructions, Likert response scale, and scoring method for the NM module are identical to the Generic module, with higher scores indicating a better health-related quality of life [13].

2.4. Data analysis

Agreement between telephone administration and in-person administration for the Generic and NM modules for child self-report and parent proxy-report was determined through intra-class correlation coefficients (ICC). ICCs and 95% confidence intervals (CI) were calculated using a one-way random effects analysis of variance model for reliability of telephone administration and reliability of scoring. ICCs are designated as <0.40 poor to fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 good agreement and 0.81–1.00 excellent agreement [17,18].

3. Results

A total of 20 children with SMA were recruited for telephone administration of the PedsQL™ Generic and NM module. From previous study visits, 18 subjects were familiar with the Generic module, and 7 of those also had experience with the NM module. Participants were children ages 8–17 and parents of children 2–17 at one clinical center. The average age of the 11 boys (55%) and 9 girls (45%) was 8.4 years. With respect to ethnicity, 2 (10%) participants were Hispanic and 18 (90%) were Non-Hispanic. In terms of race, 0 (0%) participants were Black/African-American, 14 (70%) White and 6 (30%) Other. Four (20%) were diagnosed with SMA Type I, 8 (40%) with SMA Type II and 8 (40%) with SMA Type III. The mean interval between the in-person and telephone administration was 2.82 days (median 2, range 1–7 days). Six participants were in the age range of 2–4 and were administered the report forms for toddlers. Five participants were in the age range of 5–7 and were administered the report forms for young children. Four participants were in the age range of 8–12 and were administered report forms for children. Five participants were in the age range of 13–18 and were administered report forms for teens.

The ICCs and 95% CI for the reliability of telephone administration for different comparisons is shown in Table 1. The number of forms completed for each comparison is included in the table. The numbers are dissimilar as not all participants completed every form during both the in-person and telephone visits for the following reasons: (1) children under the age of 8 were not able to participate in telephone administration, (2) either the parent or child was not available during the allotted window, or (3) time constraints. There was excellent reliability among telephone and in-person administration (ICC: 0.923; 95% CI: 0.876–0.952) (Fig. 1). The reliability for groups assigned to telephone interview before or after their in-person visit did not differ significantly. The NM module, including both parent and child forms, was slightly more reliable (ICC: 0.958 95% CI: 0.915–0.980) (Fig. 1) than the Generic module (ICC: 0.857 95% CI: 0.733–0.926) (Fig. 1). The reliability of the child forms, including both Generic and NM modules, (ICC: 0.865 95% CI: 0.720–0.938) and the parent forms (ICC: 0.911 95% CI: 0.839–0.952) were similar. Inter-rater reliability for scoring was also excellent (ICC: 0.992 95% CI: 0.981–0.997).

4. Discussion

This study supports that the PedsQL™ Generic and the NM modules can be administered reliably over the telephone to SMA patients and their caregivers. This finding would be expected to reduce missing outcome data that has compromised previously reported SMA clinical trials [3,14,15]. Notably, the telephone administration is reliable in children as young as 8 years. The child-report forms designed for those 5–7 years old should be administered by reading the instructions and each item to the young child word for word. A separate page with the three faces response choice is used to help the young child understand how to rate their response. To avoid caregiver or parental bias during telephone administration, the child reports for this age group was not included in this study. Excellent scoring reliability of telephone administration also was demonstrated in 8 patients.

A large proportion of missing data is likely to be related to the burden imposed on patients and families by in-person study visits. Outcomes that can be reliably ascertained remotely can reduce missing data. A recent study concluded that children had similar interpretation of the items on the Generic module regardless of mode of administration [16]. This population included 533 healthy and chronically ill children ages 5–18 years. Those findings supported the factorial invariance of the Generic module across in-person, mail and telephone surveys. Factorial invariance means that participants of in-person, mail and telephone administration answered the items in a similar manner, such that the operationalizations of the psychological constructs are similar across groups. This contribution to empirical literature on the PedsQL™ demonstrates strong factorial invariance for child self-report across mode of administration [16].

Other modes of administration have been explored recently. The use of web-based questionnaires for the PedsQL™ Generic shows promise. Data suggested that 8–13 years old children with chronic health conditions do not provide different health information online when compared to information provided on pencil and paper. This study established the reliability and validity of web-based questionnaires for self-report by children with chronic health conditions [19].

Outcome measures that can be administered via telephone would be less burdensome, and minimize missing important data collection. Future clinical trials in this population may use in-home monitoring to longitudinally study patients, requiring fewer visits to the clinic. This move towards in-home assessment using feasible and safe measures will minimize patient and family burden in research participation. It is anticipated that observations done during in-home assessments and alternative modes of administration (i.e. telephone, online, mail) for quality of life instruments will provide sufficient data to allow for fewer clinic visits. Research conducted in a clinic setting has been the standard format for clinical trials. However, the family burden of in-hospital testing and the limited capacity of clinical research centers can make frequent visits impractical. Telephone administration of outcome measures addresses several of the limitations of clinical trials in SMA. Quality of life measures can be obtained over the telephone, avoiding family burden and missed visits.

The finding that children with neuromuscular disorders and their parents evidenced imperfect agreement between self-report and proxy-report is consistent with documentation in the health-related quality of life measurement of children with and without chronic illness, suggesting information provided by parents is not equivalent to that reported by the patient [20,21].

This study was designed to determine if telephone administration provided a reliable alternative to meaningful data collection from children and parents who have barriers to participation in traditional research. Although the relatively small sample size of our study is a potential limitation, we were able to demonstrate excellent reliability between the two modes of administration. In a relatively rare disease like SMA, it would require additional effort and resources, and likely multiple study sites to enroll a large group of participants into an observational study. A challenge for this study was the execution of complete randomization of participants receiving telephone administration of the PedsQL™ before their clinic visit. Due to these unequal group sizes, an unbalanced randomization was used in the later part of the study. A group of 12 patients were able to be reached prior to the visit. We found this study design was feasible and resulted in good reliability of telephone vs. in-person administration.

Another challenge of this study was language barriers. The PedsQL™ Generic and NM modules were administered in English over the telephone to two parents whose primary language was Non-English. Because further explanation of the items was required beyond the script to permit a response from the parent,

Table 1
Comparisons for all modules and forms including generic (G), neuromuscular (NM), for parent (P) and child (C). Intra-class correlation coefficients and 95% confidence intervals for the reliability of telephone administration. *N* is the number of forms included in each comparison. The number varies as not all modules and forms could be obtained at all visits in both parents and children.

Comparison	<i>N</i> (forms)	ICC	95% CI
Phone vs. in-person visit (All modules and forms: G, NM, P and C)	65	0.923	0.876–0.952
Phone <7 days before visit vs. in-person visit (All modules and forms: G, NM, P and C)	33	0.935	0.872–0.967
Phone <7 days after visit vs. in-person visit (All modules and forms: G, NM, P and C)	33	0.923	0.850–0.961
Generic module phone vs. in-person visit (G for P and C)	34	0.857	0.733–0.926
NM module phone vs. in-person visit (NM for P and C)	31	0.958	0.915–0.980
Child report phone vs. in-person visit (G and NM for C)	25	0.865	0.720–0.938
Parent report phone vs. in-person visit (G and NM for P)	40	0.911	0.839–0.952

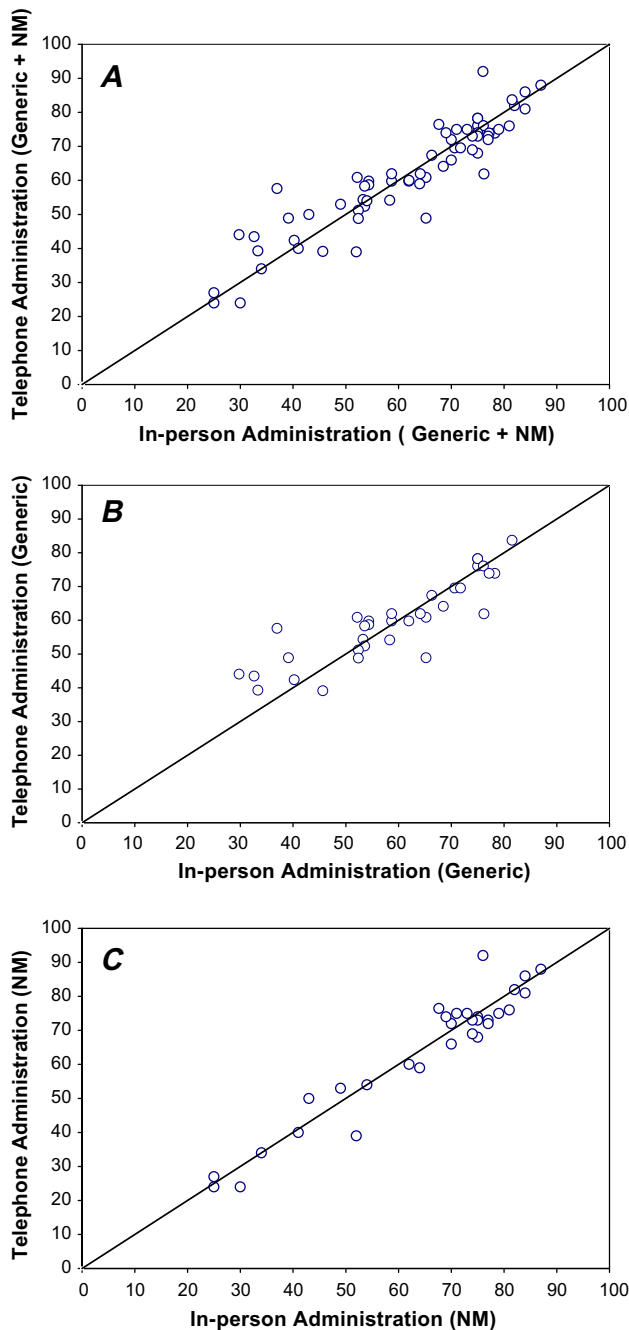


Fig. 1. Scatter plot of telephone vs. in-person administration of the PedsQL™ Generic module and the NM module. Straight line indicates perfect reliability. Axis' represent total scale score. Modules and forms abbreviations: generic (G), neuromuscular (NM), parent (P) and child (C). (A) Phone vs. in-person visit: all modules and forms G, NM, P and C. (B) Generic module phone vs. in-person visit: G for P and C and (C) NM module phone vs. in-person visit: NM for P and C.

we excluded questionnaires from these two parents from the analysis. Future directions and suggestions for further research include obtaining a larger sample size, creating assessments of inter-rater and test-retest reliability for administration and having language interpreters trained in administration of the PedsQL™. There are multiple existing translations in a complete set of the Generic module. Translations of the NM module should undergo linguistic validation to allow use with families whose primary language is Non-English.

For the purposes of a clinical trial, administration of the PedsQL™ Generic and NM modules over the telephone would provide an integrated measurement model with the advantages of both generic and condition-specific instruments. Telephone administration can be used to improve the efficiency of data collection, enhance the feasibility of multisite research projects and result in a more inclusive sample by facilitating the inclusion of children with barriers to traditional research participation. This finding of excellent reliability of telephone administration of the PedsQL™ Generic and the NM modules in the context of a multicenter clinical trial adds to their favorable properties as outcome measures in SMA clinical trials.

Acknowledgments

This work was supported by the SMA Foundation. The suggestions of James W. Varni, Ph.D., Texas A&M University, College Station, TX were particularly valuable. Dr. Varni holds the copyright and the trademark for the PedsQL and receives financial compensation from the Mapi Research Trust, which is a nonprofit research institute that charges distribution fees to for-profit companies that use the Pediatric Quality of Life Inventory. We gratefully acknowledge the families and children who participated in this study.

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