A new frontier in Health-Related Quality of Life (HRQoL): the EuroQol Toddler and Infant Populations (EQ-TIPS)

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Abstract

Background The EQ-TIPS is an experimental instrument to measure and value the HRQoL in children aged zero to three years. The initial development of EQ-TIPS took place in South Africa with subsequent work ensuring a multi-national focus. This paper describes the consultation with global experts and caregivers which aimed to a) review the wording and content of the EQ-TIPS descriptive system to ensure global relevance and suitability across the age range; b) assess the need for additional dimensions; c) explore the challenges associated with measuring HRQoL in the youngest populations.

Methods Three groups, consisting of; experts in HRQoL (n = 26), experts in child health and development (n = 27) and caregivers of children aged zero to three years (n = 65) participated in online surveys. Experts were recruited through snowballing. Previously consented caregivers from Australia and members of an international paediatric intensive care group were invited to participate. Data was analysed by thematic analysis.

Results The EQ-TIPS was well received by experts and caregivers. Participants acknowledged the benefits EQ-TIPS would bring to clinical practice, health research and policymaking. The emphasis on health economic decision-making was highlighted "*without a good HRQoL measure, economic evaluation in children focuses on 'lives saved' which then ignores morbidity*". There was limited consensus amongst experts regarding the use of the term 'age-appropriate' within the EQ-TIPS framework "*[There] needs to be some understanding of where a typical child would/ should be developmentally*". An alternative term 'age appropriate' was suggested with universal acceptance of the term 'age-appropriate'. Concern was highlighted regarding the perceived overlap between 'social interaction' and 'communication'; and whether in their currently worded forms they are distinct enough to warrant being separate dimensions. Furthermore, respondents questioned whether the dimensions are sensitive enough to account for the nuances of a child's sense of self "S*ocial interaction is very different across children. . . some might be just very shy and cautious, and others might embrace other people very quickly*". Additional dimensions suggested for further investigation at the multi-national level were sleep and emotional functioning, "*I think its [EQ-TIPS] pretty close to being optimum. I just wonder about sleep*". Experts and caregiver responses highlighted the complexity of proxy report "*It is not just the differences in children's health, but also [the] differences in the reporting approach [of the caregivers]*". It was suggested that introducing examples across all dimensions would decrease this subjectivity and reduce the global differences in perceptions of dimensions.

Conclusion Further multi-national development of the EQ-TIPS will be informed by ongoing input from experts and caregivers. The suggested changes to the descriptive system will be tested qualitatively in a multi-national program of work that follows. Future work will target samples across cultural and ethnic groups, geographical regions, socio-economic status and the age range to further explore the content validity of the EQ-TIPS and to determine the youngest age which we can reliably measure HRQoL on the EQ-TIPS.

Introduction

The provision of social care and healthcare is coming under increasing global pressure. Providing and delivering safe, effective, and quality care is becoming increasingly constrained in an era of rapidly changing healthcare and economic environments (1). The routine, systematic and longitudinal use and collection of information through patient reported outcome measures (PROMs) or Observer-reported Outcomes (ObsROs) has been seen as a mechanism to for decision making the clinical and health economic environments. (2,3,4). PROMs and ObsROs are designed to assess various dimensions of an individual's health and wellbeing (5,6). PROMs can be completed by self-report or proxy-report whereas ObsROs rely solely on proxy-report. Beyond evaluating the effectiveness of treatment(s) in a clinical trial context, PROMs and ObsROs are used to; facilitate provider-patient relations in clinical care; quality improvement in evaluating healthcare provider performance; guiding initiatives to progress healthcare; and evaluate the effectiveness of healthcare interventions in the context of population health research (5,7). The use of PROMs/ObsROs has been shown to not only enhance quality of care and decision making in routine healthcare but also in being able to identify best practices needed to improve health outcomes through tracking health and disseminating outcomes (8). This can inform clinicians of the variability between patient/ community groups, provide information on the value patients place on their health status and to predict patient outcomes (2,3,4).

Despite the high burden of disease seen in children under the age of three years, few ObsROs exists that are specifically designed to evaluate the HRQoL of children within this age group (9). There are currently 20 generic ObsROs available for evaluating the HRQoL of children under the age of three (9). However, only three of these measures are amenable to elicitation of preference-weighted scores; the Health-Related Quality of Life Utility Measure for Pre-School (HuPS) (formerly *the Health Status Classification System for Pre-School Children (HSCS-PS))* (10,11), Infant Quality of Life Instrument (IQI) (12,13,14), and the EuroQol Toddler and Infant Populations (EQ-TIPS) (formerly the *TANDI)* (15,16,17). The aforementioned PROMs have been identified as generic preference-weighted measures designed with an existing value set in place or the potential to generate one (18). The HSCS-PS developed in Canada and Australia was developed from the Health Utilities Index (HUI) for children aged 2.5-5years two to four years (19). The initial 12 items were reduced to eight and mapped to that of the HUI for development of the HuPS and its associated preference-weighted score. (20,21,19). The IQI, was created using a multinational sample from China-Hong Kong, UK, USA, New Zealand, and Singapore for children aged one to twelve months (21). Considering the seven health attributes included it remains unclear whether the IQI age range could be expanded as items may not be applicable to older children (12,13,14). The EQ-TIPS was developed *ab initio* in South Africa and modelled on the EQ Family of instruments (16,15). The instrument was developed for children aged zero to three years and includes six dimensions of health. As with all EuroQol instruments it is amenable to generating a preference-weighted value set.

Limited availability of ObsROs for use in young children reinforces the need for the continued development of the EQ-TIPS. As the EQ-TIPS was initially developed in South Africa, ongoing stakeholder engagement on a global scale is crucial to ensure multi-country and multi-country validity of the instrument.

Involving key stakeholders in all phases of research is pivotal for the effective and equitable availability of PROMs/ObsROs in health and social care settings. In research and clinical settings, actively engaging with end-users, caregivers, and practitioners is imperative in the decision-making processes regarding ObsROs/ PROMs development, selection, and implementation (1,22). Approaches to stakeholder engagement in PROM/ ObsROs development vary significantly across research, health, and social care settings. Previous studies indicate limited stakeholder engagement, often involving only clinicians (23) or patients (24) and less frequently both (25,26). Incorporating patients and/ or proxies perspectives ensures PROMs/ObsROs remain patient-centred (27,28)

Methods for stakeholder engagement typically include training, surveys, qualitative focus groups/workshops and quality improvement processes (25,23,26). Ensuring strategic and thorough engagement in PROM/ObsRO development through a multi-national cross-cultural stakeholder engagement is crucial for ensuring relevance, comprehensiveness, and comprehensibility (29,30). This holds true for the EQ-TIPS which was initially developed in South Africa; ongoing stakeholder engagement on a global scale is an essential stage in the development of the final instrument. Thus, this study aimed firstly to engage stakeholders to ensure the global relevance of EQ-TIPS across various cultural and ethnic identities. The second and third aims of the study included assessing the applicability of the EQ-TIPS to the zero to three-year-old age group and different disease categories and to identify the challenges associated with measuring HRQoL in this age group.

Methodology

i. Participants and Data Collection

Ethical approval for the study was granted by the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (HREC: 307_2022). The online survey, hosted by REDCap, was designed for participants to provide feedback on and insight into the descriptive system of the EQ-TIPS. Separate surveys were therefore designed to tap the expertise and experience of three groups: 1) experts in HRQoL, 2) experts in child health and development and 3) caregivers of young children. The surveys were developed by the research team and content was tested independently by a minimum of two expert EuroQol members who were external to the research team. The surveys were pilot tested with post graduate health economics students before final distribution.

Respondents for the online survey were recruited through snowballing, with the research team requesting the distribution of the invitation to colleagues and/ or friends. The initial invitations to participate were distributed to those with EuroQol Membership and to personal contacts of the research team. Caregivers of children aged zero to three years from the Quality of Life in Kids: Key Evidence to Strengthen Decisions in Australia (QUOKKA) Study, International Paediatric Intensive Care Network who had previously consented to participating in further research and contacts of the study team were also invited to take part in the study. The inclusion criteria included having the capacity to provide written responses in English, access to a stable internet/ WIFI connection and ability to complete the approximately 25-minute online survey (link 1).

To provide potential participants with the necessary background information to be able to navigate through the online survey, they were provided with access to a short animation accessed through *Vimeo* (link 2) and access a Google Drive (link 3) with published EQ-TIPS literature prior to completing the survey. Consenting participants were given four weeks in which to complete the survey. There was no reimbursement for participation.

ii. Data Analysis

The open-ended questions included in the online survey were analysed qualitatively using a thematic approach including inductive and deductive reasoning. Close-ended questions were quantitatively analysed by calculating the frequency of close-ended responses.

In line with the six phases of thematic analysis outline by Braun and Clark (31), analysis was carried out by two members of the research team (JV and EB), who met periodically to discuss the findings at the completion of each phase to ensure consistency and agreement regarding the analytical interpretations.

A coding framework was agreed upon by both researchers. Participant responses to the open-ended questions from the online survey were attributed to a node and/ or sub-node and subsequently used to support the summation of a narrative summary of the results (Online Supplement - Table 1: Deductive and Inductive Matrices with Examples).

iii. Data Management

Participant responses were anonymous and no identifying information was included in the analysis. Some participants did voluntarily provide their contact information to be contacted for further EQ-TIPS research opportunities. Any identifying participant information was kept separate from the data for the analysis. The data will be retained for 10 years after publication.

Results

Sample

A total of 118 participants completed the online survey. Fifty five percent (n = 65) of respondents were caregivers, with the remaining 23% (n = 27) and 22% (n = 26) of respondents self-identifying as experts in Child Health and Development and HRQoL, respectively. Ninety seven percent (n = 63) of caregivers identified themselves as parents, while the remaining 3% (n = 2) self-identified as carers. The Asia-Pacific region (Australia, China, Fiji, India & New Zealand) accounted for 57% of respondents' country of work/ residence. Africa (Ethiopia, South Africa & Zimbabwe), Europe (Germany, Hungary, Ireland, Netherlands, Sweden & UK) and The America's (Brazil, Canada, Colombia & USA) accounted for 18%, 12%, and 12% of the country of work/ residence identified by respondents, respectively (Table 2).

Table 2. Participant Demographic Information.

	HRQoL Expert		**Child Health and Development Expert**		**Caregiver**	
	n = 26		*n* = 27		*n* = 65	
	n	%	*n*	%	*n*	%
Country of Residence/ Work						
Australia	2	8%	6	21%	55	77.5%
Brazil	1	4%	-	-	-	-
Canada	-	-	2	7%	2	2.8%
China	-	-	1	4%	-	-
Colombia	-	-	1	4%	-	-
*Europe**	7	27%	-	-	3	4.2%
Fiji	1	4%	-	-	-	-
India	1	4%	1	4%	-	-
New Zealand	1	4%	-	-	-	-
South Africa	5	19%	13	46%	8	11.3%
United Kingdom	3	11%	2	7%	-	-
United States	3	11%	2	7%	3	4.2%
Zimbabwe	1	4%	-	-	-	-
Primary Work Role						
Academic Researcher	21	80.8%	3	10.7%	-	-
Clinician/ Health Professional	-	-	20	71.4%	-	-
Education Specialist	-	-	5	17.9%	-	-
End User of HRQoL Instruments	2	7.7%	-	-	-	-
Pharmaceutical Company	2	7.7%	-	-	-	-
Contract Research Organisation	1	3.8%	-	-	-	-
Experience working and/ or raising children under 3 years						
Yes	18	72%	28	100%	-	-
No	7	28%	0	0%	-	-
Children of their own	-	-	-	-	68	97.1%
Cares for Children	-	-	-	-	2	2.9%

Europe includes; Germany, Hungary, Ireland, the Netherlands, and Sweden.*

1. Overall Impression

The EQ-TIPS was well received by all caregivers and expert stakeholder groups. Most respondents acknowledged the substantial benefits associated with the EQ-TIPS in relation to primary care surveillance, clinical practice, interventional and applied health research, and policymaking. There was further commendation on developing new content for the measure and not merely adapting the existing EQ-5D-Y.

> *". . . without a good HRQoL measure, economic evaluation in children focuses on 'lives saved' which then ignores morbidity".*

> *"A very necessary instrument for measuring HRQoL in this young age group, which is often overlooked in HRQoL research. Easy and quick to use".*

> *"I enjoyed the additional description of the dimensions, which is different to the EQ-5D-Y or adult versions"*

Participants had varied views on the clarity of the EQ-TIPS overall. While some appreciated its concise and clear language, providing a comprehensive overview to valuing a child's health, others expressed concerns about the subjective interpretation and preconceived ideals around typical health, development progression and the future (Online Supplement – Table 1).

> *"Comprehensive representing major elements of what we would perceive health, simple and quick to use. . ."*

> *[Expert in HRQoL] "As a parent the dimensions analysed make sense to me. I also believe a caregiver familiar with a pre-verbal child will be able to ascertain them".*

> *"Difficult for parents who were anticipating a normally developing child to give a percentage as to how their child's health is . . . As a physiotherapist . . . I may think they are doing quite well but for a parent who may not know what the future holds in the early days they may feel their child is not doing well health wise".*

2. Proxy Reporting

As the age range for the EQ-TIPS is zero to three years completion is dependent on a proxy respondent who completes the measure based on observable behaviours related to the child's health condition. Experts and caregiver responses highlighted the complexity of proxy report.

> *"It is not just the differences in children's health, but also [the] differences in the reporting approach [of the caregivers]".*

Responses showed the primary concern regarding the use of proxies centred around two primary themes: 'contamination' of child's actual health status and 'diversity of development' evident in this age group.

> *"The proxy perspective is the biggest challenge. . . differences in the reporting approach of the parents, which may "contaminate" the actual health status. Furthermore, children in general, but especially under*

> *the age of three, may have very different development status, which could also bias the reporting of the health status".*

Expert and caregiver responses expressed uncertainty about whether a child's caregiver is the most appropriate proxy respondent. Responses highlighted general concern around caregiver experience and knowledge, family structure, environmental dynamics, and a child's communicative capacity as influences on proxy reporting.

> *"Parent responses may be biased; significantly varied levels of language development and verbal comprehension in this age group, combined with varying abilities, concentration, and attentiveness, could be attributed to any number of factors - environmental, learning opportunities, etc - parents' knowledge of the norm for child developmental markers may vary also".*

Respondents suggested multiple alternatives to act as a proxy on the child's behalf: teachers, nannies, primary care physicians, and/ or therapists.

HRQoL expert responses cited the heterogeneity in proxy responses to a variation in normal development as a cause for concern and in particular the reference to 'age-appropriate' could prove challenging to proxies to assess a latent trait at a fixed level.

> *" Development rate is so variable and important activities change rapidly as the child ages. One is also dependent on the report of a proxy who has to rely on the external*

3. Content Validity – Relevance, Comprehensibility, Comprehensiveness

i. Age Appropriate

Currently the EQ-TIPS dimensions, except the dimension of pain, uses norm referencing and compares the behaviour of other children of a similar age when selecting responses. This is done with referring to the age-appropriateness of the behaviour. Respondents from both expert groups were critical of a caregiver's ability to understand the appropriateness and applicability of the term 'age-appropriate' in the context of the EQ-TIPS.

> **"***There needs to be some understanding of where a typical child would/ [should] be developmentally . . ."*

Responses from both expert groups critiqued the caregivers' potential understanding of 'age-appropriate' in the context of lack of knowledge surrounding paediatric development, diversity of development, and the emotional burden associated with valuing their child's own health status.

> *". . . Age-appropriateness could also lead to an emotional burden for parents as proxies when being confronted with their child's inabilities".*

> *". . . However, I do find it a bit confusing when answering, thinking about my youngest child who is three-months old. It is difficult to know if I should answer by comparing her to other children the same way or answer if she has problems . . ."*

Whereas caregivers overall understood the term ‘age-appropriate’ with relevant examples and responded more positively to its reference within EQ-TIPS.

> *“. . . relates to the age of the child and what is reasonable to expect from your child based on what other children of the same age are doing”.*

ii. Response Levels and Recall Period

Respondents across stakeholder groups showed low completion rates for questions on response levels and recall periods. Most participant responses favoured the current three-level system, whereas others were in favour of using a four or five-level system,

> *“The fact that there are only three levels for the answers (no, some, a lot) is very useful as parents may not be able to ascertain beyond that”.*

However, some participants suggested improving the severity scale for clarity of context.

> *[Child Health and Development Expert] “. . . maybe for some problems and a lot of problems, put a % ([for example,] 50% of the time or 90% of the time)”.*

Experts in HRQoL (n= 12) and Child and Health Development (n= 8) found the recall period ‘TODAY’ suitable.

> *“Children's health is very fluctuating and often changes from day to day… I think that the use of "today" would result in a more reliable answer”.*

In contrast, some experts expressed reservations about the appropriateness of the recall period considering the lability in this age group.

> *“These young children fluctuate so much from day to day. A minimum of a few days would be needed to get an idea of overall HRQOL rather than just on the day. . .”*

> *“It was a little problematic for the pain dimension as it quickly changes within the day, while communication for example is more stable over time”.*

i. Dimensions

The EQ-TIPS currently includes five dimensions namely: movement, play, pain, social interaction, communication and eating. Generally, dimensions currently included within the EQ-TIPS were considered by both expert groups and caregivers to be appropriate, relevant, and applicable to children under the age of three.

> *“Comprehensive, represents major elements of we would perceive health [to be], simple and quick to use . . .”*

Although the dimensions were widely accepted, respondents suggested there is a need for increased utilisation of examples across the six dimensions.

> *“. . . moves about is quite broad. some examples of what would constitute each level would be good. e.g. what does major issues look like vs some issues”.*

The absence of examples was noted as increasing the subjectivity of proxy judgements and therefore makes judgements about certain dimensions more susceptible to proxy bias.

> *“Is this item about the capacity of movement, the child’s development? [e.g.,] being able to sit, be able to crawl”.*

a. Movement (*Moves about at an age-appropriate level)*

Analysis showed split consensus amongst expert groups regarding the relevance of the ‘movement’ dimension as it is currently worded. Respondents who were critical touched on the age of the children and lack of terminological specificity and subsequent caregiver comprehension as a negating factor. In contrast, those who responded favourably discuss the relevance of movement across the life span.

> *“. . . For a two or three-year-old, movement would be very important and therefore extremely appropriate, but for a zero-six-month-old it might be less relevant for their HRQoL”.*

> *"Like most skills, fine and gross motor skills are vital to a child’s development and things may impede this (even temporarily) can have long term consequences”.*

The lack of specificity in the term ‘movement’ and reference to ‘at an age-appropriate level” was considered by some to be a strength of the questionnaire and by others to decrease the comprehensiveness of the EQ-TIPS.

> *“. . . Even if you describe movement as moves for an age-appropriate level, I wonder if parents or caretakers understand what is meant by age-appropriate because there is always a ‘range’”.*

> *“Movement is a broad enough term to encompass . . . development of movement from early head and arm control through to walking and running in older children”.*

Both expert groups further acknowledged the vital carry-over effects of movement on a child’s environmental and social learning development.

> *“Movement is essential to exploration. . .”*

Caregivers with children across the age-range were able to understand movement as a dimension, and readily able to provide appropriate examples of problems associated with movement.

> *“Problems with reaching, grabbing, articulation of body etc".*

b. Play (*Enjoys playing with objects or toys at an age-appropriate level)*

Play as a dimension was considered by both expert groups and caregivers to be relevant to the measurement of HRQoL, and applicable across the age range of zero to three years. Respondents acknowledged that ‘play’ has the potential to serve as an indicator of a child’s developmental progression.

> *"Play is integral to a child's development and a key component of HRQoL. It is a child's primary form of social interaction and exposure to the world. No child I have ever met dislikes playing - whether that be alone or with others!"*

However, responses did acknowledge that the comprehensibility of play is undermined by the passive and active nature of play, variation within the age-range and potential physical or mental impairments.

> *"Children with [a] disability may not be able to play age-appropriately".*

Suggestions were made to include age-appropriate examples for key developmental stages to reduce the subjectivity in proxy reporting.

> *"Type of play may vary; however, it is appropriate across all ages. It may be valuable to have a short description of play as it is relevant to each age/developmental level, particularly newborns".*

Caregivers of children across the age range could instinctively perceive play as a dimension and easily provide an example of potential challenges within the dimension.

> *"Inability to play independently or with other children. Sensory overload or lack of evidence of sensory input (sight, hearing, touch). Distress".*

c. Social Interaction (*Engages with others in an age-appropriate manner)*

The relevance of including 'social interaction' in the EQ-TIPS was criticized by HRQoL experts. In contrast experts in child health and development highlighted the importance of early identification for long term mental health outcome and the role of interventions across this young age group.

> *"I am uncomfortable with the inclusion of 'social' dimensions in self-reported measures of HRQoL, because they are heavily dependent on external factors other than health care. In the context of young children, the (undeniable) importance of this dimension is surely derived from its impact on development (rather than the present experience of the health state)".*

> *"[Social Interaction is an] early indicator of divergence from typical development which correlates strongly with future [HR]QoL-related problems e.g. [autism spectrum disorder] ASD is strongly associated with pre-adolescent mental health issues".*

> *"Many [Child and Adolescent Mental Health Services] CAMHS and therapies are effective in supporting social interaction meaning this is highly changeable and relevant as an outcome measure".*

Experts and caregivers did however all expressed concerns regarding the lack of specificity in the current wording of this dimension particularly concerning the definition of social interaction, determining age-appropriate social interaction, and addressing neuro and physically diverse children in the age range.

"I may see a child with a severe disability socially interacting age-appropriately within their physical ability. . . but not at an appropriate level for their age".

"Maybe it is not applicable to babies less than six-month-old but it certainly is after that age as they become more aware of the social world around them".

Furthermore, respondents questioned whether the dimensions are sensitive enough to account for the nuances of a child's sense of self.

"Social interaction is very different across children. . . some might be just very shy and cautious, and others might embrace other people very quickly".

However, experts and caregivers acknowledge that social interaction plays a critical role in a child's emotional, intellectual, neurological, and physical development and wellbeing.

"Important as this may indicate 'normal' social development (e.g., no eye contact or verbal interaction may be an indication of learning or developmental concerns)".

"Although I think social interaction may change from family social interaction in infants to other children and people outside the family as they infant gets older, I think social interaction is similarly important across those [age] groups".

Caregivers with children across the age-range seemingly had good comprehension of problems with 'social interaction' with appropriate descriptions of behaviours that may be observed.

"No eye contact, no smiling or interest in others."

d. Communication *(Communicates at an age-appropriate level)*

Overall, the inclusion of communication was considered relevant for the measurement of HRQoL and applicable across the age range by most respondents. Respondents acknowledged children's communication abilities, regardless of age, encompasses verbal and non-verbal cues.

"In my experience, all toddlers are able to communicate - if not verbally, then through crying and gesturing. The inability to do so almost always signals that something is wrong - either the child is acutely ill (e.g., infection, teething), or impaired neurologically".

"I currently help care for my nieces . . . but even as young as six months, they were able to express content, frustration, or hunger through their demeanour and actions".

There were concerns raised about dimension comprehensibility and potential overlap between communication and social interaction as currently worded.

> *“. . . communication is important for HRQoL. . . is already a part of social interaction. . . not sure how this will add value”.*

> *“It [social interaction] needs to be clearer and more distinct from “play” or “communication”. In my mind, “social interaction” conflates the other two dimensions”.*

Caregivers across the various age range groups were able to instinctively grasp communication as a dimension and readily able to provide examples of problems associated with communication.

> *“Not being able to convey what they need, whether that’s by a baby crying or a toddler not being able to express in words how they are feeling”.*

e. Eating (*Eats adequate available food in an age-appropriate manner)*

Eating was acknowledged as a key determinant in the development, growth, and health of children across the entire age range. Analysis showed eating was nearly universally accepted amongst respondents as relevant to HRQoL and applicable across the age range.

> *“Eating seems like a vital function of the child. Usual eating patterns may change due to illness and revert back to normal afterwards. If, however, the child stops eating for a longer period that is going to be a huge concern”.*

Questions arose regarding the comprehensibility of the item, as currently worded, and how it would account for normal variation in eating during childhood e.g., picky eating or children with a small appetite. This further highlighted concern with the subjectivity of reporting problems.

> *“Some children do not like to eat certain vegetables for a period of time. Is that having some problems with eating, or can it be considered normal for that age group?”*

> *“. . . one parent may report that their child is a picky eater or has a small appetite, has ‘no problems eating’. . . However, another parent may report the same issues in their child as ‘some problems eating’”.*

Suggestions made by respondents to expand the scope of examples provided to included alternative methods of feeding e.g., Percutaneous Endoscopic Gastronomy (PEG), Naso-jejunal Tube (NJ Tube). Further suggestions were made to clarify that feeding included breast/ bottle feeding as forms of eating.

> *“. . . however, some children will receive PEG feeding that may or may not impact [HR]QOL – would this be included in this dimension? Or is this relating to oral feeding? . . .”*

Caregivers were able to provide appropriate examples of what problems with eating may entail for children of all ages.

> *"Inability or difficulty swallowing, tongue ties, uncoordinated mouth movements, inability to chew, oesophageal difficulties, vomiting. . . indigestion, reflux . . .gasping, choking, visible discomfort getting food down".*

> *"Not gaining weight, tired, listless, further health problems associated with malnourishment".*

f. Pain (*Painful behaviour includes: inconsolable crying restless movement, grimacing)*

The relevance of including pain in a HRQoL measure was noted by all groups with an overwhelming acknowledgment that parents could identify pain across the age group.

> *"Pain is a relevant factor for HRQoL, and I think that's something that a proxy will be able to answer easily".*

While verbal articulation of pain might be challenging/absent for children in this age range, experts and caregiver responses recognised there are non-verbal behaviours associated with experiencing pain.

> *"Pain is a symptom and a sign no matter of the age; if we cannot verbalise it doesn't mean it doesn't exist".*

The subjective nature of interpreting a child's pain, raised additional concerns with expert groups about distinguishing pain from other forms of discomfort and caregiver burden.

> *". . . Parents burdened with the care of a child in pain might however overestimate the true feeling of pain".*

However, caregiver responses highlighted the subjective yet nuanced understanding of a child's pain, with examples including persistent crying, impaired movements, withdrawal, and specific facial expressions.

> *". . . Parents can almost always pinpoint when a child is in pain by the type of crying/ movement the child is experiencing".*

g. Missing dimensions

Participants from both expert groups offered a number of suggestions for dimensions which may be beneficial to include in the EQ-TIPS. The most frequent suggestions included sleep and emotions or mood.

> *"I think its [EQ-TIPS] pretty close to being optimum. I just wonder about sleep. . ."*

> *"Poor sleeping patterns do have an impact on the child's development and functioning, as well as on the well-being of the caregivers. . ."*

Discussion

The need for ongoing development of the EQ-TIPS was affirmed by expert groups and caregivers alike as they applauded the development of the EQ-TIPS and acknowledging the need for ObsROs in this age group. There was further support of using the EQ-TIPS not for the description of health in this age group in health economic decision making indicating that preference weighted values would be beneficial. Although maintaining the structure of the EQ-5D family of instruments contributed to the ease of use the *ab initio* development of the EQ-TIPS and subsequent departure from the five dimensions included on the EQ-5D adult and youth instruments (32) was seen as beneficial. This deviation in content between instruments may prove challenging in the future when comparing health state between age groups and/or when young children transition between instruments, for example, in longitudinal analysis. The importance of developmental appropriateness of the instrument versus the transition between instruments warrants further debate with stakeholders.

Further key issues warranting in depth discussion and debate were highlighted by responses from key stakeholder groups: 1) acknowledging external factors influencing proxy report and subsequent strategies to reduce the bias introduced with proxy reporting and 2) inclusion of reference to age-appropriate behaviour currently included in the EQ-TIPS. While study respondents acknowledged the lack of alternative to proxy reporting in this age range concerns emerged regarding who should act as the proxy and the potential for proxy or caregiver bias in the current version of the EQ-TIPS.

It was noted that the parent may not be the most appropriate proxy to complete the EQ-TIPS. As the completion of the EQ-TIPS relies on recall of observable behaviours the person spending the most time with the child may be the most appropriate proxy. Suggestions of alternative proxy respondents included but were not limited to teachers, clinicians, nannies, or family members. The primary caregiver of the child may be influenced by cultural and geographical factors and it is suggested that in lower-middle-income-countries (LMICs) this would likely include extended family or community members whereas other settings may rely on a teacher or nanny for childcare (33,34). Evans et al. (35) highlighted a proxy’s emotional involvement and neutrality levels should also be considered for their impact on responses. The nature of proxy reporting will to a certain extent, introduce some level of subjectivity into the study. However, it becomes of greater concern when the basis of the proxy’s interpretation of the dimension(s) is impacted by other critical variations, including age range and the wide range of normal deviations from what is typically anticipated from a proxy’s perspective.

The comparison of children’s behaviour or functioning to an age-appropriate norm was identified by both expert groups to be the primary contributor to subjectivity. Cross cultural studies have shown that there may be large differences between and within cultures on parental knowledge of childhood development. This disparity in knowledge together with socio-economic circumstances and level of education may impact not only parenting style but interpretation of health and development (36,37,38). Respondents further highlighted that attainment of key milestones for gross motor, fine motor, personal-social and speech function may have high variability. This wide range of normal development in childhood is supported by findings in the literature and is postulated to be influenced by genetics, environment, experience and socio-culture context (39).

Comprehensibility is arguably difficult to test in an online survey however, caregivers did interpret the dimensions correctly and were able to give appropriate examples of what behaviours may be associated with problems in each dimension. Interpretation of the relevance of these problems for the specific age of the child was beyond the scope of this study. Although respondents suggested that adding examples of observable behaviours to the description of each dimension may improve comprehensibility this warrants further discussion with caregivers and parents of very young children to establish if comprehensibility will be improved.

The inclusion of the EQ severity response scale for this young age group has been highlighted as ambiguous and a further potential source of subjectivity. One of the respondents indicated that a frequency scale may better understood and scored by caregivers. Peasgood et al (40) emphasise response options can revolve around the frequency of occurrence a symptom or problem occurs, or the severity of the associated symptom/ dimension. The process utilised by respondents in determining a numerical value to qualitative response options like those seen in frequency (e.g., 'often, 'sometimes', 'seldom') and severity (e.g., 'very much', 'quite a bit', 'sometimes') scales is not clearly understood (40). Additional evidence suggests the interpretation of response options could be heterogeneous within different population groups, more specifically regarding their health, language, and cultural background (41). The response scale and recall period are inextricably linked and a frequency scale may arguably be better suited to a longer recall period than today. Shorter recall periods have been criticized for underestimating the symptom burden, particularly evident in conditions where symptoms fluctuate diurnally or on a day-to-day basis (42). This criticism is likely to be as relevant in the period of infancy and toddlerhood but may be further compounded by their general lability which is intrinsic to their life stage and not their health state. The recall period of 'today' arguably does not account for this normal deviation in behaviour but for assessment of acute changes in health or with repeated measures in children with chronic or latent health conditions it may provide a more accurate description of a child's health status, despite this lability (43).

The relevance of the social interaction dimension was questioned by experts in HRQoL. This may be inextricably linked to the comprehensibility of this dimension as many comments highlighted the difficulty in identifying behaviours that may be associated with problems related to social interaction and the overlap between social interaction and communication as currently presented. Social interaction in infancy is critical for brain development as these social experiences subsequently contribute to the development of communication skills (44). Some literature aligns social interaction or relationships to non-verbal skills whereas in older children, who develop verbal skills, verbal communication may also be integral to social interaction (44). These items need to be operationalised so that they are both well understood by caregivers and measure the most appropriate constructs. The construct of social interaction is also a direct indicator of emotional development in young children and was included in the EQ-TIPS on this basis (45). However, it is apparent that this is not currently well understood or accepted as an item to evaluate mood or emotions was suggested to increase the comprehensiveness of the EQ-TIPS. The understanding of the interplay between social interaction and emotional development needs further interrogation with experts and caregiver. Seemingly the construct is important to include but the operationalisation for children aged zero to three years is currently inadequate.

The current dimensions in the EQ-TIPS were largely considered relevant for measuring HRQoL in toddlers. However, in general the relevance of the dimensions was less certain for infants, particularly those younger than six months of age. The large amount of time young children spend sleeping allows for less time for caregivers to observe behaviours. There is further a low repertoire of movement observed in the first 6 months due to the immature nervous (46). This makes judgement of observable behaviours in young children challenging. Other instrument developers have further highlight that a large variation in age ranges proves challenging as skills may not be pertinent at all ages (12).

Sleep was further highlighted as an important dimension to consider for inclusion. Young children spend a large amount of time sleeping to support their growth and development. Sleep requirements decrease in age with infants typically sleeping for 80% (+/-17 hours), those aged four months to one year; one to two years and over three years requiring on average 12-16 hours, 11-14 hours and 10-13 hours of sleep respectively (46). Sleep is well documented to be imperative for brain maturity and functioning thus poor sleep would significantly impact the infant or toddler’s HRQoL (46). Experts from both groups cited the impact lack of sleep and subsequent impact on development and functionality would significantly impact their relative HRQoL. However, respondents also acknowledged the potential interaction between sleep and existing EQ-TIPS dimensions; pain and eating. Correlations between sleep and HRQoL dimensions of psychological wellbeing, school environment, and social interactions with peers was documented for children aged three - ten years (47). Additional evidence shows inadequate sleep negatively impacted a child's cognitive and emotional capacities, as well as their ability to engage socially with peers and friends (47). Sleep problems in children under five years have been associated with poor behaviour, worse school performance and obesity (46). Poor sleep at this age is well documented to negatively impact caregiver and family HRQoL (46). Sleep, sleep hygiene, good sleep environment and sleep routine is complex and changes during the life course. Sleep is a complex construct, and accurately assessing it can be challenging. Objective evaluation of sleep and caregiver reporting of sleep issues may pose difficulties in achieving objectivity and may limit the feasibility of inclusion in the instrument. Further discussion with stakeholders and caregivers on the inclusion of sleep is warranted.

Limitations

Several limitations are pertinent to this study. Firstly, the recruitment strategy, relying on the research team’s professional network and advertisements, may give rise to introducing self-selection bias, as participants with specific interests or connections to the team may be more likely to participate. This could impact the generalizability of findings to a broader population. Secondly, the data collected through an online survey may be constrained in depth and interpretability, potentially limiting the richness and nuance of responses compared to more in-depth qualitative methods. In the current study, this proved a limiting factor for respondents whose first language was not English. Finally, the geographical representation of participants may not be fully comprehensive potentially affecting the generalizability of the study's findings. While the study provides valuable insights, these limitations should be acknowledged when interpreting and applying the results.

Conclusion

Further multi-national development of the EQ-TIPS will be informed by ongoing input from experts and caregivers. The suggested changes to the descriptive system will be tested qualitatively in a multi-national program of work that follows. Future work will target samples across cultural and ethnic groups, geographical regions, socio-economic status and the age range to further explore the content validity of the EQ-TIPS and to determine the youngest age which we can reliably measure HRQoL on the EQ-TIPS.

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