

# Interactive role-playing and health-related quality of life assessment in children with neurocognitive sequelae: A global neuroethics research approach



Vasiliki Rahimzadeh<sup>a</sup>, Gillian Bartlett<sup>b</sup>, Cristina Longo<sup>b</sup>, Judy Illes<sup>c</sup>

<sup>a</sup>Postdoctoral Fellow, Stanford Center for Biomedical Ethics, Stanford University, Stanford, CA, United States, <sup>b</sup>Department of Family Medicine, McGill University, Montréal, QC, Canada, <sup>c</sup>Neuroethics Canada, Department of Neurology, University of British Columbia, Vancouver, BC, Canada

*Physicists are perfectly right in stressing the difficulties of research into elementary particles. But they should not resent being told that such research is child's play in comparison with the scientific comprehension of games played by children! The rules of any game are only a conventionally marked path; children "run" along this path very capriciously, violating its borders at every turn, because they possess free will and their choice cannot be predicted. Nothing in the world is more complex or more perplexing than a human being.*

**—On the Human Being and Being Human, A. Spirkin**

## Introduction

In this chapter, we explore the practical and theoretical strengths of role-playing games (RPGs) as a method to understand health-related quality of life (HRQoL) in children with neurodevelopmental and cognitive sequelae (NDCS) resulting from brain cancer. We call attention to proxy reporting in empirical studies and its effects on the body of HRQoL knowledge upon which care strategies in the pediatric NDCS population are largely based. This chapter is among the first to promote the gamification of HRQoL research, and in particular RPGs as an engagement-oriented research and clinical data collection tool for children with NDCS. The theoretical underpinnings of HRQoL through role-playing as they manifest through functional forms of play among children with NDCS are described in depth, including the practical strengths and challenges thereof. In landscaping the history and practice of HRQoL research with children, we echo the observation that the “research community has lacked the expertise, imagination and capability to engage the most disabled (especially children) in research processes that can genuinely capture their experiences and enable positive and emancipatory changes

to result (Hodge, 2008)” (Simmons, 2014). The methods and outputs of role-playing can be used as an adjunctive, patient/child-centered information tool for clinical decision-making in the NDCS context in specific. Our intent is to propose an RPG that is amenable to adaptation in HRQoL research and shared decision-making involving neurodiverse children and their families more broadly. Role-playing games as HRQoL research methodology abandon categorical assumptions of vulnerability—including for children with life threatening/limiting disorders—which too often mask children’s exclusion from research behind a protectionist bioethical rationality.

We appreciate that brain cancer may not always lead to neuropsychiatric disorders, but significant overlap exists with neurocognitive disorders when depression (Buchbinder et al., 2017), difficulty sustaining peer relationships (Vannatta, Gerhardt, Wells, et al., 2007) and other psychosocial sequelae involving cognitive functioning evolve following cancer diagnosis or during treatment. With game-play as a borderless and ubiquitous, although not socially or socioeconomically-neutral phenomenon, we conclude this chapter with potential applications to other fields of pediatric research inquiry, contexts and populations. Such potential contributions to research methodology in neuroethics and brain and mental health disorders make RPGs truly global in their clinical application across care and research contexts involving children. In the section to follow, we discuss the research-care nexus unique to pediatric oncology, the clinical successes therein, and the accentuated need to improve HRQoL research among children diagnosed with, as well as survivors of childhood cancer.

## **At the nexus of tumor research, care and survivorship**

Brain tumors and other nervous system cancers constitute one of the leading causes of cancer-related death in children (Fitzmaurice, Allen, Barber, et al., 2017), while childhood epilepsy represents the greatest burden of disease post treatment for childhood brain- or other CNS tumor (Feigin, Abajobir, Abate, et al., 2017; Kenborg, Winther, Linnet, et al., 2018). This finding is documented worldwide, although data are most readily available for middle and high income countries (Howard, Davidson, Luna-Fineman, et al., 2017). Evidence-based standards of care are problematized by both the relative rarity of cancer in children, and the stringent regulatory norms of involving vulnerable populations such as neurodevelopmentally disabled children in research. The implications of knowledge lacunas resulting from children’s exclusion from research is perhaps best illustrated in oncology. Dosing regimens for many anti-cancer therapies, for example, are extrapolated from studies conducted with adults, and can be highly toxic when administered to children (Feinstein, Morrato, & Feudtner, 2017).

Pediatric oncology is among the few specialties where therapeutic opportunities are afforded through both standard care and participation in clinical research. Survivorship following childhood cancer now exceeds 80% in high-income countries thanks in large part to highly coordinated research networks and international cancer consortia that offer patients opportunities to participate in clinical trials and share trial data (Pui, Gajjar, Kane, et al., 2012). The completion of the Human Genome Project in 2003, as well as subsequent advances in the “omics” disciplines have, in

turn, expanded clinical research and translational science opportunities. These include cancers with genetic predispositions to neurodevelopment and other behavioral disorders. The Human Genome Project also had the effect of reconfiguring the very nature of research participation and associated benefit-risk calculi; as research participation increasingly constitutes the collection, analysis, and sharing of children's genomic and associated clinical data, informational risks, in addition to physiological risks, become chief ethical considerations.

The effects of expanding such research opportunities are likewise tangible in the pediatric brain- and CNS tumor field. The involvement of children in clinical and genomic research is at an all-time high (Dufetelle, Jong, & Kaguelidou, 2018; Surun, Dujaric, Aerts, et al., 2018),<sup>a</sup> and clinical databases such as ClinVar and dbGaP make aggregate genomic and associated clinical data involving children available to researchers and clinicians alike. Access to linked genotypic and phenotypic data from children diagnosed with brain and other cancers have already resulted in significant improvements to individual patient diagnosis and care in what scholars define as learning healthcare systems (Institute of Medicine et al., 2007).<sup>b</sup> Indeed, convergence of research and clinical care (Wolf, Amendola, Berg, et al., 2018) are defining attributes of the learning healthcare system “that is designed to generate and apply the best evidence for the collaborative healthcare choices of each patient and provider; to drive the process of discovery as a natural outgrowth of patient care” (Institute of Medicine et al., 2007).

Overall survival at 1 and 2 years post diagnosis, however, remain dismal for children with brain gliomas specifically (Hassan, Pinches, Picton, et al., 2017) despite the advances that learning healthcare systems and broader access to linked clinical data have together ushered in. This situation persists also despite vast improvements in 5-year survival rates for many other pediatric cancers, accentuating the need to optimize HRQoL<sup>c</sup> both during, and post treatment for brain and other tumors of the central nervous system (CNS) (Engelen, 2011).

Of adolescent and young adult cancer survivors, the prevalence of NDCS is highest among those with brain and other CNS tumors (Forrest et al., 2014; Hocking, Hobbie, Deatrick, et al., 2011; Stone, Waern, Khabra, et al., 2017). This population

<sup>a</sup> Although participation rates are steadily increasing, nonpublication bias remains a scientific concern. Crockett and colleagues note that among registered phase 3 randomized controlled trials, nearly a third (29%) go unpublished.

<sup>b</sup> Learning healthcare systems are meant to transcend patient populations and geographies, yet some example of such systems specifically geared towards improved learning in pediatric settings have been developed (see for example, Forrest, Margolis, Seid, et al., 2014).

<sup>c</sup> Although not an uncontested construct, HRQoL is generally accepted to encompass “functional effects of a medical condition and/or its consequent therapy upon a patient...[and] is thus subjective and multidimensional, encompassing physical and occupational function, psychological state, social interaction and somatic sensation” (ISOQOL, What is Health-Related Quality of Life Research). The Healthy People 2020 project further clarifies the features of quality of life that make it explicitly health-related: “When quality of life considered in the context of health and disease, it is commonly referred to as HRQoL to differentiate it from other aspects of quality of life. Since health is a multidimensional concept, HRQoL is also multidimensional and incorporates domains related to physical, mental and emotional, and social functioning” (Healthy People 2020, 2019).

has specific difficulties in executive functioning and lowered IQ, among other developmental and behavioral challenges. Studies also report lower HRQoL across several indicators when compared to other pediatric oncology populations (Penn, Shortman, Lewis, et al., 2010; Schulte, Russell, Cullen, et al., 2017; Varni, Burwinkle, Sherman, et al., 2005; Wolfe, Orellana, Ullrich, et al., 2015) and youth with chronic conditions (Barakat, Hobbie, Minturn, et al., 2017; Hobbie, Ogle, Reilly, et al., 2016). Quast et al. attribute these poorer HRQoL outcomes in part to ongoing and additional anti-cancer therapy (Quast, Phillips, Li, et al., 2018).

Precision oncology is furthermore shedding new light on the “omics” etiologies of childhood brain and other cancers and contributing to longer life expectancies as a result (Goudie, Coltin, Witkowski, et al., 2017). Consequently, the population of pediatric brain tumors survivors is growing, albeit not for all children, everywhere (Phillips, Padgett, Leisenring, et al., 2015). Disparities in cancer cure rates between low/middle and high-income countries are cause for grave concern. Whereas “in high-income countries (HIC), 75% of children with cancer are cured...over 80% of the world’s children live in [low income countries], in which cancer cure rates often do not exceed 35% (Fitzmaurice et al., 2017; Vannatta et al., 2007). Even more unfortunate is the fact that the gap in survival between children with cancer in LIC versus HIC continues to widen as curative therapies are developed in the latter but not implemented in the former” (Bao, Zheng, Wang, et al., 2009).

The availability of quality data suggesting increases in cancer survivorship is attributable largely to standard reporting and monitoring of global pediatric cancer trends by organizations such as the International Agency for Cancer Research—a specialized subsidiary of the World Health Organization—and the International Classification of Disease Oncology, respectively. Incidence and prevalence data on pediatric brain and other CNS tumors are predominantly reflective of European and North American populations (Storm, Engholm, Mägi, et al., 2017), while comparable data from low and middle-income countries (LMIC) are limited (De Robles, Fiest, Frolkis, et al., 2015; Ezzat, Kamal, El-Khateeb, et al., 2016; Frazier, Piñeros, Fuentes, et al., 2017). The evolving areas of unmet need among children living with NCDS are exacerbated in LMICs that lack specialty care services and resources for longitudinal patient management (Howard et al., 2017). Frazier et al. (2017) highlight such discrepancies in available data across the Global North and South. The authors describe the significance of cancer registries and classification in LMICs towards accurately assessing the burden of disease related to such childhood cancers on a global scale (Bastos, Silveira, Luna, et al., 2017; Frazier et al., 2017). A lack of regional diversity in the clinical genomic databases mentioned earlier further constrain possible inferences into etiologies of childhood cancer across global contexts.

Studies assessing the impacts of NDCS on HRQoL, especially in the face of refractory disease in LMICs, is also markedly scant (Bhat, Goodwin, Burwinkle, et al., 2005; Stone et al., 2017; Tock, Bhat, Szymonifka, et al., 2014). In one of the only systematic reviews of its kind, Macartney et al. note 16 empirical studies investigating HRQoL in pediatric brain cancer survivors, and identified 10 heterogeneous HRQoL instruments (Macartney, Harrison, VanDenKerkhof, et al., 2014). The authors note that “[...] while some instruments captured individual symptoms, only three studies

explored the relationship between symptoms and HRQL outcomes. Although there is a negative relationship between pain, fatigue, and HRQL reported in the literature, the relationship between other symptoms and HRQL is unknown (Macartney et al., 2014).” Recent studies have since highlighted the need to investigate longitudinal HRQoL factors in this population (de Ruyter, Schouten-van Meeteren, van Vuurden, et al., 2016; Demers, Gélinas, & Carret, 2016), including fatigue (Tomlinson, Zupanec, Jones, et al., 2016), physical activity (Devine, Mertens, Whitton, et al., 2018; Paxton, 2010), and anxiety (Lazor, Tigelaar, Pole, et al., 2017) among others. Schulte et al., in a more recent meta-analysis discovered that survivors of pediatric brain and other CNS tumors experience poor HRQoL up to 25 years following treatment. For this reason, future research is needed to correlate leading NDCS with brain tumor diagnosis to improve prognosis and HRQoL for childhood cancer survivors (Schulte et al., 2017).

The situational vulnerability of children diagnosed with, or survivors of cancer in LMICs is hence compounded. First, a cancer diagnosis is relatively rare when compared to other health conditions, e.g., communicable and chronic diseases that may be more prominent in LMICs. These children are, secondly, further disadvantaged when their home countries are ill-equipped to provide treatment options and follow up on any NDCS that may result from their cancer.

## Instrumentalizing and globalizing HRQoL research

While a nascent field of inquiry in the medical humanities, HRQoL research methodology has remained relatively preserved. Armstrong (2009) provides a useful historical analysis of HRQoL as a methodological construct in medical research from 1970 to 2007. He writes about an empirical turn in the early 1990s that made HRQoL “a vague idea into a measurable ‘fact’; quality of life made the transition from rhetorical concept to a hard end-point of clinical practice.” (Armstrong, 2009). Measurement and quantification of HRQoL stood in stark contrast to the phenomenological and ethnographical research that preceded this empirical turn, and which at its height in the early 1960s and 70s was driven by qualitative health research giants including Glaser, Strauss, Bluebond-Langner and others (Bluebond-Langner, 1978; Glaser & Strauss, 1965).

HRQoL research in the decades to follow progressively standardized and quantified HRQoL indicators, supplanting much of the psychosocial orientations that prior sociological and anthropological research typified. This empiricist turn in part gave rise to quantitative HRQoL instruments including the European Quality of Life Group-5D (European Quality of Life Group, 2009). Perhaps the widest HRQoL instrument used today is the EQ-5D domain measures of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Respondents rate the degree to which they perceive problems related to each HRQoL domain in the questionnaire on a 3- or 5-level severity scale.<sup>d</sup>

<sup>d</sup> In 2009, the EuroQol Group launched a specific instrument for youth (EQ-5D-Y) that included identical dimensions of analysis but in developmentally appropriate wording suitable to younger populations (e.g., mobility; looking after myself, doing usual activities; having pain or discomfort and feeling worried: sad or unhappy).

Although instruments have been developed to assess HRQoL facilitators, barriers and patient-reported outcomes in children (Leahy, Feudtner, & Basch, 2018; Varni & Limbers, 2009), including in global mental health contexts (Drotar, 1998; Matza, Swensen, Flood, et al., 2004; Penn et al., 2010; Solans, Pane, Estrada, et al., 2008), nearly all such instruments are modified from those developed for use in adult populations. Moreover, even pediatric-specific HRQoL instruments take on both the form and function of adult instruments, which often probe children using questionnaires that involve cognitive tasks like rating, rationing and risk-benefit assessments. While meant to be pediatric-specific, these instruments appeal to adult-oriented logics, rationalities and reasonings that children either may not have fully grasped as yet, or are wholly incapable of performing due to their neurodevelopmental or behavioral condition. The Medical Research Council report on Medical Research Involving Children confirms this:

*Standard outcome measures in adults include death and quality of life, but for many conditions different outcomes are more relevant. Measurements of these outcomes have been determined for use in adults specifically and may not be relevant for children. Quality of life measures can be used, but should be focused on the child or family and validated and tested for reliability and responsiveness to change before being used; such instruments have not always been available. It is therefore useful, and important, to consult children about outcome measures and other issues, when the research is being designed (Medical Research Council, 2004).*

The methodological turn towards quantifying indicators and patient-reported outcomes in the early 1990s greatly influenced the body of HRQoL knowledge that was produced. Bjornson and McLaughlin (2001) corroborate this trend in HRQoL measures involving children with cerebral palsy: “HRQL measures may have been designed to serve one or more of three possible functions: discrimination, prediction and evaluation” (Bjornson & McLaughlin, 2001). The authors go on to define three primary purposes of HRQoL measures: a discriminative measure intended to distinguish between quality of life among children with different clinical characteristics, a predictive measure to estimate future outcome or prognosis; and an evaluative measure to indicate change in a characteristic over time (Bjornson & McLaughlin, 2001). Below, we describe a fourth, emerging category—experiential—that aims to contextualize children’s HRQoL experiences not as a discreet measure, but rather as illness narratives. First, however, we call special attention to parent and health professional proxy reporting in HRQoL research with children, its effects on existing bodies of HRQoL knowledge, and how models of shared decision-making in the pediatric neuropsychiatric space inevitably takes up such knowledge.

### **Proxy-reporting in HRQoL research**

Whereas past quantitative, qualitative and mixed methods studies have investigated various dimensions related to quality of life among childhood brain tumor patients and survivors, findings are overwhelming based on parental or clinician proxy reporting. Furthermore, many empirical studies assess late effects of pediatric brain and

CNS tumors after patients reach adulthood (Sato, Higuchi, Yanagisawa, et al., 2014). Delaying this research is a missed opportunity for preventing negative NDCS early in remission, and while patients are still young. Proxy reporting can be entirely appropriate, even necessary in some circumstances where the child is nonverbal, or perhaps suffers from severe NDCS that makes even adapted modes of communication difficult or impossible (Varni & Limbers, 2009; Varni, Limbers, & Burwinkle, 2007a). Researchers have therefore paid considerable attention to assessing interrater consistency between proxy- and patient-reports, albeit with mixed success, in effort to improve internal and external validity of HRQoL research that relies on proxy reporting (Cremeens, Eiser, & Blades, 2014; Matza et al., 2004; Meeske, Katz, Palmer, et al., 2004; Morrow, Hayen, Quine, et al., 2012; Sattoe, van Staa, & Moll, 2012; Solans et al., 2008; Theunissen, Vogels, Koopman, et al., 2014; Varni, Limbers, & Burwinkle, 2007b).

Proxy-reporting raises several key theoretical and practical limitations even under conditions of high interrater consistency. The individual HRQoL dimensions that such instruments assess—usually in the form of questionnaires—are predetermined by adults, and furthermore presented within a strictly status-based as opposed to an experiential frame. That is, patients and proxies report only discreet dimensions of HRQoL the instrument of choice outlines, e.g., mobility, pain or discomfort, feelings of worry, and without contextual appeal to what or how, if at all, such dimensions are meaningful to the child. Such instruments can delimit what is otherwise a vast expanse of HRQoL themes that may be relevant to patients and their families, including the meaning patients and proxies ascribe to these themes. Absent attention to the significance of meaning, researchers cannot expect to capture the social phenomena of HRQoL that we, and others, believe guide a child's illness experience. A combination of HRQoL data collection and analytical methods are needed therefore to produce relevant knowledge that is attuned to both the experiential and status-oriented dimensions of HRQoL to inform meaningful HRQoL interventions.

Consider for example the scenario in which patients and proxies achieve high interrater coherence on perceived feelings of fatigue, a common item on many conventional HRQoL assessment tools. It might be that child and proxy agree on the perceived status of the child's fatigue based on observable behaviors such as time and quality of sleep. But without moving beyond characterizing the status of fatigue, and towards contextualizing the global effects that fatigue may have on behaviors, practices, and abilities that can together define how children perceive their own quality of life, it is questionable whether child-proxy rater coherence provides meaningful guidance on how to mitigate fatigue in efforts to enhance HRQoL.

The decision making processes underpinning these, and other interventions, for children with NDCS, and the HRQoL knowledge used to support preferred interventions, are among the research-practice nexuses that role-playing games can feasibly create in the pediatric neuropsychiatric context. We are at times critical of the quality of children's engagement in shared decisions in this space, where HRQoL interventions for children suffering from NDCS may be based solely on information gleaned from proxy-reports, or from instrument-mediated HRQoL results. These decisional inputs alone can be problematic considering the empirical limitations explained above, to say nothing of the opportunities to facilitate children's participatory agency they

inevitably miss. Such empirically limited HRQoL assessments are further problematic in LMICs, where medical paternalism may dictate child-patient-clinician behaviors and maxims of decision-making (Park & Cho, 2017). We support the position, however, that the ethos of shared decision making that can result as a positive byproduct of HRQoL research which prioritizes children's meaningful involvement is "entirely consistent with the priorities of low income settings—that is, to improve health literacy, improve patient provider communication, and empower individuals to be more involved in their healthcare (Stiggelbout, Van Der Weijden, De Wit, et al., 2012)."

Based on our above review of the unique clinical presentations among children living with NDCCS, as well as the methodological features of HRQoL research involving them, NDCCS post pediatric brain tumor diagnosis and treatment are diverse, frequent, and understudied from a HRQoL perspective; this is moreover a consistent research gap across low, middle and high-income countries. We elaborate in the subsequent sections twin neuroethical and empirical priorities that RPGs can fulfill in the global mental health and HRQoL research communities to enhance participatory mechanisms of knowledge production and translation.

## **Expanding the game-research nexus through role-playing in HRQoL**

### ***Rights to the game***




Role-based research methods used to explore contextually-grounded themes of HRQoL accepts the premise that HRQoL is both interactive and relational. Researchers can capture the richness of children's HRQoL through the illness narratives that children tell during role-based interactions, as well the meaning children attribute to various dimensions of HRQoL. The research-care nexus needed to comprehensively capture the HRQoL narratives and clinical needs of this patient population thus requires an innovative research engagement approach that too adopts an interactive and relational orientation to HRQoL. Role-playing as an empirical tool is, to be sure, not novel. It has been used extensively to further the understanding, for example, of childhood development in education (Johnson, 2007; Wong, Odom, Hume, et al., 2015) and developmental psychology (Corsini, 2017; Landreth, 2012) among many others, yet fewer initiatives have combined role playing and HRQoL research, in specific (Barrera, Atenafu, Sung, et al., 2018).

RPGs, we believe, fulfill twin neuroethical and empirical priorities. They activate children's rights to participation in understanding issues that directly concern them, rights codified in international conventions such as the United Nations Declaration of Human Rights, the United Nations Convention on the Rights of the Child (UNCRC) and outlined under special conditions in national regulations governing the protection of human research participants (Box 1). As such, game-based research methods abandon categorical assumptions of children's vulnerabilities that too often mask their exclusion from research behind overly protectionist bioethical rationality.









RPGs privilege child-centric knowledge generation by embedding HRQoL assessment into the very communicative and interactional norms unique to children, such as functional play, and thereby fulfills an empirical imperative. Put differently, RPGs fill an empirical knowledge gap by generating and translating data on HRQoL seldom derived from the child herself. The inductive approach to data collection and analysis that RPGs afford separates game-based methods of research engagement from

### Box 1 Internationally relevant conventions, statutes and guidelines related to the participation of children in research

Document	Article/Statute related to participation in research
International Conventions UN DECLARATION OF HUMAN RIGHTS 	<p><b>Article 27</b>  <i>Everyone has the right freely to participate in the cultural life of the community, to enjoy share in scientific advancement and its benefits.</i></p>
UN CONVENTION ON THE RIGHTS OF THE CHILD 	<p><b>Article 12</b>  <i>1. States Parties shall assure to the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child.</i></p> <p><b>Article 13</b>  <i>The child shall have the right to freedom of expression; this right shall include freedom to seek, receive and impart information and ideas of all kinds, regardless of frontiers, either orally, in writing or in print, in the form of art, or through any other media of the child's choice.</i></p>
International Guidelines CIOMS—INTERNATIONAL ETHICAL GUIDELINES FOR RESEARCH INVOLVING HUMANS 	<p><b>Justification of the involvement of children and adolescents in health-related research.</b>  <i>The participation of children and adolescents is indispensable for research into diseases of childhood and conditions to which they are particularly susceptible, as well as for clinical trials of drugs that will be used for children and adolescents as well as adults</i></p> <p><b>Order of Involvement in Research</b>  <i>The current Guidelines do not require that research first be conducted in adults if the research includes interventions that have a prospect for potential individual benefit for children and adolescents. This prospect is sufficient to justify the risks associated with the interventions and procedures, provided that the cumulative risk of all study interventions and procedures that do not have a prospect of potential individual benefit are no more than minimal. If research meets these conditions but the cumulative risk of all study interventions and procedures that do not have a prospect of potential individual benefit is only a minor increment above minimal risk, then research ethics committees must be convinced that the research is of special relevance to children or adolescents and could not be carried out equally well in an adult population. In such cases, older children who are more capable of giving assent must be selected before younger children or infants, unless there are sound scientific reasons for performing the research in younger children first.</i></p>
WMA DECLARATION OF OTTAWA ON CHILD HEALTH	<p><b>4. Research &amp; monitoring for continual improvement includes:</b></p> <ol style="list-style-type: none"> <li>1. All infants will be officially registered within one month of birth.</li> <li>2. All children will be treated with <b>dignity and respect</b></li> <li>3. Quality care is ensured through on-going monitoring of services, including collection of data, and <b>evaluation of outcomes</b></li> <li>4. Children will <b>share in the benefits from scientific research</b> relevant to their needs</li> </ol>

(Continued)

### Box 1 Internationally relevant conventions, statutes and guidelines related to the participation of children in research—cont'd

	<p>5. The <b>privacy</b> of a child patient will be <b>respected</b>.</p>
<p>National Guidelines</p>	
<p>TRI COUNCIL POLICY STATEMENT ON ETHICAL CONDUCT OF RESEARCH INVOLVING HUMANS</p> 	<p><b>Article 4.4</b> Children shall <b>not be inappropriately excluded</b> from research solely on the basis of their age or developmental stage.</p> <p><b>Article 4.6</b> Subject to applicable legal requirements, individuals who lack capacity to consent to participate in research shall not be inappropriately excluded from research. Where a researcher seeks to involve individuals in research who do not have capacity to consent for themselves, the researcher shall...satisfy the [research ethics board] that:</p> <ol style="list-style-type: none"> <li>the research question can be addressed <b>only</b> with participants within the identified group; and</li> <li>the research does <b>not</b> expose the participants to <b>more than minimal risk</b> without the prospect of <b>direct</b> benefits for them; or</li> <li>where research entails only minimal risk, it should at least have the <b>prospect of providing benefits to participants or to a group</b> that is the focus of the research and to which the participants belong.</li> </ol>
<p>UNITED STATES COMMON RULE</p> 	<p><b>45 CFR 46 Subpart D §46.404</b> HHS will conduct or fund research in which the IRB finds that <b>no greater than minimal risk</b> to children is presented, only if the IRB finds that adequate provisions are made for <b>soliciting the assent</b> of the children and the <b>permission of their parents or guardians</b>, as set forth in §46.408.</p>
<p>MEDICAL RESEARCH COUNCIL—MEDICAL RESEARCH INVOLVING CHILDREN</p> 	<p><b>Methodological Issues</b> Standard outcome measures in adults include death and quality of life, but for many conditions different outcomes are more relevant. Measurements of these outcomes have been determined for use in adults specifically and may not be relevant for children. <b>Quality of life measures can be used, but should be focused on the child or family and validated and tested for reliability and responsiveness to change before being used</b>; such instruments have not always been available. It is therefore useful, and important, to <b>consult children</b> about outcome measures and other issues, when the research is being designed.</p>
<p>AUSTRALIAN CODE FOR THE RESPONSIBLE CONDUCT OF RESEARCH</p> 	<p><b>Research merit and integrity 4.2.1</b> The research and its methods should be <b>appropriate</b> for the children or young people participating in the research.</p> <p><b>Respect 4.2.6</b> Researchers should be attentive to the <b>developmental level</b> of children and young people when <b>engaging</b> them in understanding the nature and likely outcomes of research, and when judging their capacity to consent to the research.</p>
<p>EUROPEAN CHARTER ON FUNDAMENTAL RIGHTS</p>	<p><b>Article 24</b> 1. Children shall have the right to such protection and care as is necessary for their well-being. <b>They may express their views freely</b>. Such views shall be taken into consideration on <b>matters which concern them</b> in accordance with their age and maturity.</p>
	<p>2. In all actions relating to children, whether taken by public authorities or private institutions, the <b>child's best interests must be a primary consideration</b>.</p>

arts based or other qualitative interviewing approaches. The latter are often criticized for their overreliance on the researchers' interpretation of qualitative data, conflating the researcher and child's voice. Grounded in these twin neuroethical and empirical imperatives, we elaborate below on the theoretical and practical foundations of RPGs to study the effects of HRQoL among children with NDCS and other neurodevelopmental/behavioral disorders.

### ***Theory of the game***

It is widely understood that children are acutely aware of social orders in which they are part. One lens through which to understand *how* and *what* children understand of their social orders is by observing them play, pretend and re-enact the archetypical roles they encounter (Bowman, 2010). RPGs harness children's methods of situational awareness and self-discovery, and are classified as *functional play with pretense* according to Barton and Wolery (2008) and Barton, Choi, and Mauldin (2019). RPGs transcend two of four taxonomic categories of functional pretend play Barton and Wolery observed in children with neurological and other developmental disabilities: substitution—assigning absent attributes—and verbalization—confirmatory vocalization. Substitution through assigning absent attributes may involve using props and other representative symbols to assume the role of another, e.g., a mother, teacher or doctor, while verbalization need not require props or motor functions to role-play (Barton & Wolery, 2008; Barton et al., 2019). Another randomized trial was able to demonstrate clinically significant improvements in social skills and quality of life among children diagnosed with brain cancer using what most closely aligns with verbalization methods of role play as the primary learning intervention (Barrera et al., 2018). Based in part on this finding, verbalization methods could be better suited for children with severe NDCS who may also have limited physical/motor abilities.

Although the ability to pretend play may not always be within the cognitive capacities of some children, one study comparing free, versus structured or functional forms of pretend play among children on the autism spectrum found significantly higher levels of engagement: “When pretend play is ‘encouraged,’ ‘elicited,’ or ‘prompted,’ individuals with autism benefit from these manipulations” (Jarrold & Conn, 2011) and in turn offers support for using RPGs in the pediatric population of interest to this chapter. Bergen, citing Casby (1997), corroborates that among children with language disabilities, “actual differences in symbolic play abilities appear to be quite small; they have ‘a symbolic performance deficit more so than a symbolic competence deficit’ (p. 477). That is, their capabilities for using symbolic ideas in play may be similar to children without language disabilities. Because of their language problems, however, they are less able to make their pretense themes and roles explicit in their play” (Bergen, 2002).

Researchers may make several modifications to the RPG system itself, game materials used to facilitate role play, e.g., cards, dice or intended players in order to meet the child's communication style, level of comprehension, modes of expression or maturity commensurate with their specific NDCS. We propose two primary ways to accommodate this neurodiversity. Researchers may adopt a more rigid role-playing

structure by simplifying cognitive tasks, or by role playing with peers rather than families or clinicians to reduce power imbalances. True gamification to facilitate role play, e.g., through the use of computers, smart phones, digital graphics, and other media may also be useful modifications to traditional RPGs for children who demonstrate a preference toward technologically mediated social interactions.

We contend that RPGs in general have the ability to pique children's desire for functional forms of play, while simultaneously providing unique windows into their situational and sociocultural consciousness. Here we adopt Vygotsky's rendition of functional play as the theoretical scaffold for role-gamification of HRQoL assessment, and to better meet the therapeutic goals of children living with NDCS, neurodevelopmental and other behavioral disorders:

*...the mistake of many accepted theories [of play] is their disregard of the child's needs – taken in the broadest sense, from inclinations to interests, as needs of an intellectual nature – or, more briefly, disregard of everything that can come under the category of incentives and motives for action. We often describe a child's development as the development of his intellectual functions, i.e., every child stands before us as a theoretical being who, according to the higher or lower level of his intellectual development, moves from one age period to another. Without a consideration of the child's needs, inclinations, incentives, and motives to act – as research has demonstrated – there will never be any advance from one stage to the next. I think that an analysis of play should start with an examination of these particular aspects. It seems that every advance from one age period to another is connected with an abrupt change in motives and incentives to act. What is of the greatest interest to the infant has almost ceased to interest the toddler. This maturing of new needs and new motives for action is, of course, the dominant factor, especially as it is impossible to ignore the fact that a child satisfies certain needs and incentives in play; and without understanding the special nature of these incentives, we cannot imagine the uniqueness of that type of activity we call play.*

*(Vygotsky, 1967)*

The potential to nuance children's incentives and motives for action that are knowable through RPGs, motivates our proposal to use play as a foray into explorations of their HRQoL. By gamifying HRQoL assessment in this way, we mean to apply gaming elements and user experience principles to redesign the terms of engagement (Deterding, Sicart, Nacke, et al., 2011). Gamification is most often discussed when transforming human-human interactions into human-computer ones. Gamification of behavior change is among the fastest growing applications of game-based techniques in the health and wellness sector. Games that aim to increase physical activity among youth have been especially popular (Johnson, Deterding, Kuhn, et al., 2016; Primack, Carroll, McNamara, et al., 2012). Johnson et al. found in a systematic review of game-based interventions that several randomized controlled trials embedded HRQoL along with other patient-reported indices in game designs (Johnson, Deterding, Kuhn, et al., 2016). No study included in the review, however, reported using games to study HRQoL as a primary, as opposed to secondary, endpoint, suggesting an untapped opportunity to explore gamification of HRQoL assessment, generally, and in a specific pediatric population with whom HRQoL research is comparatively limited (Matza, Swensen, Flood, et al., 2004).

## Rules of the game

RPGs may either be person- or technologically mediated; either can be preferable depending on the cognitive abilities and resources of the players involved. For the remainder of this chapter, we focus on the design elements of a face-to-face, card-based RPG, otherwise known as a tabletop role playing game as described by Cover (2010). Tabletop role-playing games, according to Cover, unfold like a “radio drama [where] only the spoken component of a role is acted. Players may not always speak exclusively in-character but act out their role by deciding and describing what actions their characters will take within the rules of the game” (Rilstone, 1994; *Tabletop Role Playing Games*, 2014).<sup>c</sup> As is customary of other table-top role playing games from which the RPG we propose is inspired (Cover, 2010; NISE Network, 2018), we use physical character cards to assign player roles, establish the terms of the game and facilitate role-play.<sup>f</sup>

Table-top role-playing games typically occur in settings relative to the character profiles featured in the game. Hence, our RPG is meant for the actual clinical setting, a physician’s office or hospital room, for example.<sup>g</sup> Players are physically present and may include children at various stages in their cancer management—from active treatment to remission—parents, friends and other family members, treating physicians and allied healthcare providers. All players receive a character card that describes a particular role in the child-parent-clinician triad. The card provides a brief description of the role, e.g., their age, gender as well as their interests, motivations and current HRQoL status. Players assume the identity and role the character card outlines during the role play, which may or may not be identical to the role they identify with in real life. Moreover, character cards are representative of the patient populations of interest. We recommend, for instance, that character cards applicable for gameplay in the global mental health context be geographically, demographically and socioeconomically consistent with empirical trends data by the World Health Organization, UNICEF and others.<sup>h</sup> Frameworks that enable cross-cultural adaption of HRQoL measures (Guillemin, Bombardier, & Beaton, 1993) can be especially useful in this regard to inspire the clinical situations, decision-making norms and character profiles for the RPG that is fit for purpose.

In addition to players, a physical gamemaster is present, e.g., the researcher or other game facilitator who randomly assigns and distributes the character cards, serves as

<sup>c</sup> This differentiates “table-top” role playing games from “live action” role playing games in which the acting is literal.

<sup>f</sup> Cover’s volume remains the most comprehensive exploration of tabletop role playing games as a genre separate and unique unto itself in the gaming world. Her attention to the narrative and linguistic structures of tabletop role playing, and their broader implications for the construction of personal narrative is what grounds our proposal to study these narratives as they relate to experiences of HRQoL.

<sup>g</sup> Bolig outlines several conditions that optimize hospital settings as environments conducive to therapeutic forms of play and to our use of RPGs: The theoretical and practical implications of discerning the respective functions of play and attachment, the synergistic relationship between the two, and their respective contributions to mastery often underlies the issues of what are the *necessary* and *sufficient* conditions for play to occur in hospital settings” (Bolig, 1984).

<sup>h</sup> This is the approach developers of Nano Around the World adopted in designing character cards.

the arbiter of interactions between players in the game and determines when gameplay concludes. The gamemaster introduces a goal for players to achieve during the course of the RPG session based on a set of rules collectively referred to as the game system (Tabletop Role Playing Games, 2014). Once the gamemaster assigns character cards by random distribution, players share with each other the roles they are assuming in the game. Next, the gamemaster describes a clinical decision-making scenario that requires consensus from all players, a process commonly referred to as the campaign (Tabletop Role Playing Games, 2014). The scenarios provided typify actual clinical situations in which patients and families together are determining trajectories of care, in our case children living with NDCS, neurodevelopmental or other behavioral disorders. Examples of clinical scenarios in this context may involve decisions to explore treatment options that may have equivalent clinical efficacy yet different side effects with implications for quality of life; to enroll in a clinical trial that potentiates improved therapeutic benefit; or to undergo an invasive surgical procedure to hopefully improve some aspect of neurocognitive function. The game system in the RPG we propose is based on common communicative exchanges needed to reach consensus on the trajectory of care as described to us during deliberative consultations with oncologists and palliative care clinicians and where optimal HRQoL was the primary goal for terminally ill children with brain cancer.

Each player's goal is to launch a successful campaign in support of the HRQoL intervention that best meets the values, interests and priorities of their character. Players launch campaigns to optimize HRQoL in our RPG through discussion, negotiation and consensus-building in partnership with other players in the game. Over several rounds of gameplay, players advocate for their character, co-establish notions of best interests with other decision-makers, and negotiate HRQoL trade-offs between competing clinical decisions in the neurodevelopmental/behavioral context. Indeed, it is "negotiation in the [tabletop]RPG that allows for gameplay that meets a variety of interests. The TRPG as a generic form gives players agency to define the form of their game, the social interaction and the narrative that results. Whether or not the players take full advantage of this agency depends on the group. However, it is arguable that the feeling of narrative agency remains in the players' minds, even when not fully realized in action. The purpose of the TRPG is to, as a communicative act, is to foster the sense of agency over narrative" (Cover, 2010).

It is important to note that at no point in the RPG does the gamemaster cue players on how they should enact their specific roles. Likewise, player dispositions at the time of the role play necessarily direct the decisional outcomes. These game-based experiences are indeed methodological strengths because both player enactments and their HRQoL decisions should emerge inductively from the players alone absent undue influence from the gamemaster. It may therefore be relevant for the researcher to establish the child's baseline HRQoL using the instrument or approach that best aligns with the research or clinical objective the RPG is meant to supplement. A player's prior experiences and current feelings no doubt influence how they portray roles during gameplay, as well as the decisions players believe the agent they are personifying would make. It is important to note the game's outcome has no bearing on any clinical decisions facing any of the players in the immediate term. Indeed, the fictional details

of the scenario and characters are what establish safe spaces for disclosure through narrative. The RPG's fictionality thereby assuages concern that a player's disposition may inappropriately skew a relevant clinical decision either positively or negatively.

In our experience piloting the game among clinicians and researchers, game sessions may last anywhere between 10 and 30 min. The session length depends foremost on the professional background of players, the familiarity of players with the clinical scenario presented, and the initial degree of consensus or conflict in opening rounds of the game. The gamemaster can analyze myriad HRQoL themes during gameplay, such as the decisional outcome—which may differ from round to round and player to player—and the content of the discussions—via transcribing game sessions with audio visual recording.

Character cards may also be more picture-based. Graphically representing potential HRQoL interventions can facilitate participation among children with whom verbal communication is difficult. The narrative content of discussions during gameplay, such as points of agreement or conflict, as well as the ways in which players interact with each other are both analytical outputs the researcher may subsequently use as sources of qualitative data. Reaching consensus on a final decision on the trajectory of care is the primary objective of the game, but need not be the most meaningful element of gameplay as we discuss further below.

Game mechanics aside, RPGs can provide children with temporal, spatial and expressive latitude to discuss HRQoL in intimate settings and with those who are directly involved in shaping it. RPGs can serve as windows into ideal HRQoL that children living with NDCS envision and indirectly communicate through advocating on behalf of their character during the course of gameplay. As one study found, role-playing was highly effective in soliciting the views of children with behavioral challenges related to learning disability on emotional wellbeing (Hill, Laybourn, & Borland, 1996). The researchers in the aforementioned study noted how RPGs forced clinical decision makers to critically engage with the HRQoL realities children constructed indirectly through their role play enactments. Such transparent disclosure of the character's preferences, values and motives—likely inspired by the child's own preferences, values and motives—results in rich, child-centric accounts of HRQoL seldom achieved in proxy-reported, or other qualitative research approaches. Transparency on otherwise sensitive topics such as death and dying, is also the cornerstone of shared-decision making that RPGs could potentially augment.

## Limitations

Several practical and methodological factors can limit the use of RPGs in many pediatric neuropsychiatric settings. Integrating RPGs in global neuroethics contexts can be especially challenged where the continuity of health professionals, working equipment, health care compliance and literacy limit opportunities for meaningful engagement among patient-parent-clinician decision makers. Although card-based and other tabletop role-playing games are not resource-intensive, time may be a particularly limiting factor. This is especially true in large community hospital settings,

where doctor-patient ratios make prolonged patient engagement unfeasible as needed for gameplay. One potential solution may be to incorporate short game sessions into already scheduled family meetings to discuss the child's case. These meetings can be planned around critical moments/decisions in the child's trajectory of care if they are hospitalized, or as part of routine follow up or medical rounds as an outpatient as appropriate. Meaningfulness and relevance of game-playing may also be prohibitive due to the severity of the child's condition and limited health system resources to deliver on the HRQoL interventions children may identify, if at all, during gameplay (Lipstein, Lindly, Anixt, et al., 2016). While not unique to RPGs, barriers to meaningful gameplay in global mental health environments that fulfill some or all of the data collection goals outlined earlier include poor social determinants of health. Household income, education and ethnicity are strong predictors of communication efficacy and health literacy upon which the greatest utility of RPGs for assessing HRQoL related to NDCS or other mental health conditions in LMIC depend (Smalley, Kenney, Denboba, et al., 2014; Von Rueden, Gosch, Rajmil, et al., 2006).

Critics also question the authenticity of RPG simulations based on the extent to which they reflect actual communicative events in real decision-making contexts. While we accept this critique, what warrants greater appreciation is the process by which parents and clinical teams critically engage with the alternative HRQoL realities children may conceive under the structured conditions set out in the game, rather than the decisional outcome per se. Our hope is that with consistent use of functional forms of play in clinical decision-making settings, that new normative structures, processes and skillsets for community with children on how to optimize HRQoL can then be transferable to other clinical decision contexts.

## Conclusion

We elaborate in this chapter on some of the theoretical and practical underpinnings of play and their relevance to gamifying elements of HRQoL assessment in children living with NDCS. In particular, we propose role-playing as new research tool for neuroethics that can open a window into the ways children learn, self-discover and advocate for optimum HRQoL. We argue the illness narratives that unfold during gameplay affords all players—but especially children—a safe space to (i) nuance combined existential and practical features of HRQoL; (ii) better understand how stakeholders in the child-parent-clinician triad perceive their respective roles in optimizing HRQoL; and (iii) encourage collaborative problem-solving and shared decision making around HRQoL “where the disease complexity, treatment options and varying levels of evidence make [shared decision making] highly necessary” (Lipstein et al., 2016).

RPGs as a methodological tool furthermore act on rights-based protections afforded to all children as outlined in international conventions, but infrequently benefit from. As such, RPGs double as methodologically rigorous sources of empirical data on children's perceptions of HRQoL and as platforms for shared decision-making. Our application of RPGs in the pediatric neuroethics arena can achieve the latter by dismantling hierarchal decision-making coalitions most often struck between parents



and clinicians, yet less so between child and clinicians. We have observed this phenomenon in pilot phases of RPG development when clinicians are asked to assume the role of the child, and when children assume a role with more formal decision- authority such as the parent or clinician.

We appreciate that neurocognitive disorders associated with brain cancer are not necessarily neuropsychiatric, although considerable overlap exists. We use brain cancer as the test case, given the stage of development of an RPG for it. We are optimistic for the translational future of RPGs to yet more layered and complex aspects of mental health disorders, and in more resource-diverse contexts globally. Our proposal to treat RPGs as new class of participatory, game-based research methods is consistent with children's rights to be included and meaningfully engaged in civic life. Optimizing HRQoL is indeed subsumed under this participatory right and codified in international human rights conventions, research ethics guidelines and philosophical notions of self/agency that underpin the field of neuroethics (Shook & Giordano, 2014). Given the diagnostic and prognostic complexities of NDCS, RPGs transfix sensitive topics into discussable rhetorical units that may include how to overcome challenges with activities of daily living, care provider burden, or pharmacological and technological choices with uncertain clinical efficacy, among others. For mental health applications in the future, and on a global scale, stigma, acceptance, culture and values can all be included and tested in line with evolving principles of international neuroethics (Shook & Giordano, 2014).

As we discuss in this chapter, RPGs can result in two mutually beneficial outcomes for players as well as the state of knowledge on HRQoL in children living with NDCS: they provide creative, adjunctive information tools for clinicians to gain insight into oft-ignored dimensions of HRQoL, and enable HRQoL researchers to study many iterations of patient/child shared decision-making in real time. The latter is useful in the future development of clinical decision aids that embed shared decision-making and prioritization of HRQoL endpoints into the tool itself.<sup>1</sup> Rigorous data collection and analysis of gameplay sessions from myriad contexts—involving patients with varying condition severities, and across different health systems—are needed to develop and subsequently certify a clinical decision aid based on the RPG.

The benefits as well as limitations of gamifying HRQoL assessment can be transferable across clinical settings and populations. A review by Naslund et al. on m-health interventions highlights the distinct emphasis the global mental health literature places on technological scalability, especially where technologies have shown considerable therapeutic promise in under resourced settings (Naslund, Marsch, McHugo, et al., 2015). Consistent with this literature, RPGs qualify as a “technology” in both their table-top and virtual forms. Such versatility makes scaling HRQoL assessments that use RPGs adaptable to existing resources, places and populations. Table-top RPGs can

<sup>1</sup> Based on a national study of children with special health needs, Fiks et al. recommend development of clinical decision aids to promote improved communication and parent-patient-physician partnerships in caring for children with developmental and behavioral disorders. Qualitative, quantitative and mixed methods research data derived from iterations of gameplay can serve as evidence-bases upon which such decision aids can develop.

be ideal for settings where mobile devices or internet connectivity may be ubiquitous but access limited, while virtual RPGs can be adopted in settings where such resources are both readily available and widely accessible.

We anticipate that systematic data collection and analysis from game sessions across different resource and health system contexts will identify ways of improving the game to successfully overcome time and resources limitations. The cross-specialty and, more important, cross disciplinarity inherent to game-based research design and practice make the application of RPGs as it unfolds a truly integrative approach to engagement that has potential for empirical rigor, can be clinically meaningful and ethically defensible.

## References

- Armstrong, D. (2009). Stabilising the construct of health related quality of life: 1970–2007. *Science Studies (St Bonaventure)*, 22, 102–115.
- Bao, P., Zheng, Y., Wang, C., et al. (2009). Time trends and characteristics of childhood cancer among children age 0–14 in Shanghai. *Pediatric Blood & Cancer*, 53, 13–16. <https://doi.org/10.1002/psc>.
- Barakat, L. P., Hobbie, W., Minturn, J., et al. (2017). Survivors of childhood brain tumors and their caregivers: Transition to adulthood. *Developmental Medicine and Child Neurology*, 59, 779–780. <https://doi.org/10.1111/dmcn.13492>.
- Barrera, M., Atenafu, E. G., Sung, L., et al. (2018). A randomized control intervention trial to improve social skills and quality of life in pediatric brain tumor survivors. *Psychooncology*, 27, 91–98. <https://doi.org/10.1002/pon.4385>.
- Barton, E. E., & Wolery, M. (2008). Teaching pretend play to children: A review of the literature. *Topics in Early Childhood Special Education*, 28, 109–125.
- Barton, E. E., Choi, G., & Mauldin, E. G. (2019). Teaching sequences of pretend play to children with disabilities. *Journal of Early Intervention*, 41(1), 13–29. <https://doi.org/10.1177/1053815118799466>.
- Bastos, L. N. V., Silveira, J. C., Luna, C. F., et al. (2017). Childhood and adolescent cancer in the State of Pernambuco, Brazil. *Journal of Pediatric Hematology/Oncology*, 40, 1. <https://doi.org/10.1097/MPH.0000000000001017>.
- Bergen, D. (2002). The role of pretend play in children's cognitive development. *Early Childhood Research and Practice*, 4, 1–13.
- Bhat, S. R., Goodwin, T. L., Burwinkle, T. M., et al. (2005). Profile of daily life in children with brain tumors: An assessment of health-related quality of life. *Journal of Clinical Oncology*, 23, 5493–5500. <https://doi.org/10.1200/JCO.2005.10.190>.
- Bjornson, K. F., & McLaughlin, J. F. (2001). The measurement of health-related quality of life (HRQL) in children with cerebral palsy. *European Journal of Neurology*, 8(Suppl 5), 183–193. <https://doi.org/10.1046/j.1468-1331.2001.00051.x>.
- Bluebond-Langner, M. (1978). *The private worlds of dying children*. Princeton, NJ: Princeton University Press.
- Bolig, R. (1984). Play in hospital settings. In T. D. Yawkey & A. D. Pellegrini (Eds.), *Child's play: Developmental and applied*. London: Routledge.
- Bowman, S. L. (2010). *The functions of role-playing games: How participants create community, solve problems and explore identity*. Jefferson, NC: McFarland.

- Buchbinder, D. K., Fortier, M. A., Osann, K., Wilford, J., Shen, V., Torno, L., et al. (2017). Quality of life among parents of adolescent and young adult brain tumor survivors. *Journal of Pediatric Hematology/Oncology*, *39*, 579–584. <https://doi.org/10.1097/MPH.0000000000000947>.
- Corsini, R. (2017). *Role playing in psychotherapy*. Routledge. <https://doi.org/10.4324/9781351307208>.
- Cover, J. G. (2010). *The creation of narrative in tabletop role-playing games*. McFarland & Co. Publishers.
- Cremeens, J., Eiser, C., & Blades, M. (2014). Factors influencing agreement between child self-report and parent proxy-reports on the pediatric quality of life inventory 4.0 (PedsQL) generic core scales. *Health and Quality of Life Outcomes*, *4*, 58. <https://doi.org/10.1186/1477-7525-4-58>.
- De Robles, P., Fiest, K. M., Frolkis, A. D., et al. (2015). The worldwide incidence and prevalence of primary brain tumors: A systematic review and meta-analysis. *Neuro-Oncology*, *17*, 776–783. <https://doi.org/10.1093/neuonc/nou283>.
- de Ruiter, M. A., Schouten-van Meeteren, A. Y. N., van Vuurden, D. G., et al. (2016). Psychosocial profile of pediatric brain tumor survivors with neurocognitive complaints. *Quality of Life Research*, *25*, 435–446. <https://doi.org/10.1007/s11136-015-1091-7>.
- Demers, C., Gélinas, I., & Carret, A. S. (2016). Activities of daily living and quality of life in survivors of childhood brain tumour. *American Journal of Occupational Therapy*, *70*, 7001220040p1–7001220040p8. <https://doi.org/10.5014/ajot.2016.014993>.
- Deterding, S., Sicart, M., Nacke, L., et al. (2011). Gamification. Using game-design elements in non-gaming contexts. In *DI.Acm.Org*. (pp. 4–7). <https://doi.org/10.1145/1979742.1979575>.
- Devine, K. A., Mertens, A. C., Whitton, J. A., et al. (2018). Factors associated with physical activity among adolescent and young adult survivors of early childhood cancer: A report from the childhood cancer survivor study (CCSS). *Psychooncology*, *27*, 613–619. <https://doi.org/10.1002/pon.4528>.
- Drotar, D. (1998). *Measuring health-related quality of life in children and adolescents: Implications for research and practice*. Mahwah, NJ: Lawrence Erlbaum Associates.
- Dufetelle, E., 't Jong, G. W., & Kaguelidou, F. (2018). Randomized controlled trials in pediatric patients had higher completion rates than adult trials: A cross-sectional study. *Journal of Clinical Epidemiology*, *100*, 53–60. <https://doi.org/10.1016/j.jclinepi.2018.04.018>.
- Engelen, V. (2011). *Monitoring quality of life in paediatric oncology practice*. Doctoral Dissertation. University of Amsterdam.
- European Quality of Life Group. 2009. EQ-5D, <https://euroqol.org/eq-5d-instruments/>.
- Ezzat, S., Kamal, M., El-Khateeb, N., et al. (2016). Pediatric brain tumors in a low/middle income country: Does it differ from that in developed world? *Journal of Neuro-Oncology*, *126*, 371–376. <https://doi.org/10.1007/s11060-015-1979-7>.
- Feigin, V. L., Abajobir, A. A., Abate, K. H., et al. (2017). Global, regional, and national burden of neurological disorders during 1990–2015: A systematic analysis for the global burden of disease study 2015. *Lancet Neurology*, *16*, 877–897. [https://doi.org/10.1016/S1474-4422\(17\)30299-5](https://doi.org/10.1016/S1474-4422(17)30299-5).
- Feinstein, J., Morrato, E. H., & Feudtner, C. (2017). Prioritizing pediatric drug research using population-level health data. *JAMA Pediatrics*, *171*, 7–8. <https://doi.org/10.1001/jamapediatrics.2016.3462>.
- Fitzmaurice, C., Allen, C., Barber, R. M., et al. (2017). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the global burden of disease study global burden. *JAMA Oncology*, *3*, 524–548. <https://doi.org/10.1001/jamaoncol.2016.5688>.

- Forrest, C. B., Margolis, P., Seid, M., et al. (2014). PEDSnet: How a prototype pediatric learning health system is being expanded into a national network. *Health Affairs*, *33*, 1171–1177. <https://doi.org/10.1377/hlthaff.2014.0127>.
- Frazier, A. L., Piñeros, M., Fuentes, S., et al. (2017). The global burden of childhood cancer: Knowing what we do not know. *Pediatric Blood & Cancer*, *64*, 64–66. <https://doi.org/10.1002/psc.26532>.
- Glaser, B. G., & Strauss, A. L. (1965). *Awareness of dying*. London, UK: Transaction Publishers.
- Goudie, C., Coltin, H., Witkowski, L., et al. (2017). The McGill interactive pediatric OncoGenetic guidelines: An approach to identifying pediatric oncology patients most likely to benefit from a genetic evaluation. *Pediatric Blood & Cancer*, *64*, 1–5. <https://doi.org/10.1002/psc.26441>.
- Guillemin, F., Bombardier, C., & Beaton, D. (1993). Cross-cultural adaptation of health-related quality of life measures: Literature review and proposed guidelines. *Journal of Clinical Epidemiology*, *46*, 1417–14–32.
- Hassan, H., Pinches, A., Picton, S. V., et al. (2017). Survival rates and prognostic predictors of high grade brain stem gliomas in childhood: A systematic review and meta-analysis. *Journal of Neuro-Oncology*, *135*, 13–20. <https://doi.org/10.1007/s11060-017-2546-1>.
- Healthy People 2020. (2019). Health-related quality of life and well-being. In *Found Heal Meas Rep 2010*. (pp. 1–6). <https://doi.org/10.1016/j.soncn.2009.11.008>.
- Hill, M., Laybourn, A., & Borland, M. (1996). Engaging with primary school aged children about emotions and wellbeing—methodological considerations. *Children and Society*, *10*, 129–144.
- Hobbie, W. L., Ogle, S., Reilly, M., et al. (2016). Adolescent and young adult survivors of childhood brain tumors: Life after treatment in their own words. *Cancer Nursing*, *39*, 134–143. <https://doi.org/10.1097/NCC.0000000000000266>.
- Hocking, M. C., Hobbie, W. L., Deatruck, J. A., et al. (2011). Neurocognitive and family functioning and quality of life among young adult survivors of childhood brain tumors. *The Clinical Neuropsychologist*, *25*, 942–962. <https://doi.org/10.1080/13854046.2011.580284>.
- Howard, S. C., Davidson, A., Luna-Fineman, S., et al. (2017). A framework to develop adapted treatment regimens to manage pediatric cancer in low- and middle-income countries: The Pediatric Oncology in Developing Countries (PODC) Committee of the International Pediatric Oncology Society (SIOP). *Pediatric Blood & Cancer*, *64*, 1–18. <https://doi.org/10.1002/psc.26879>.
- Institute of Medicine (US), Roundtable on Evidence-Based Medicine. In L. A. Olsen, D. Aisner, & J. M. McGinnis (Eds.), *The learning healthcare system: Workshop summary* (2007). Washington, DC: National Academies Press (US). Available from: <https://www.ncbi.nlm.nih.gov/books/NBK53494/>, <https://doi.org/10.17226/11903>.
- Jarrod, C., & Conn, C. (2011). The development of pretend play in autism. In P. Nathan & A. D. Pellegrini (Eds.), *The oxford handbook of the development of play*. London, UK: Oxford University Press.
- Johnson, D., Deterding, S., Kuhn, K. A., et al. (2016). Gamification for health and wellbeing: A systematic review of the literature. *Internet Interventions*, *6*, 89–106. <https://doi.org/10.1016/j.invent.2016.10.002>.
- Johnson, J. E. (2007). *Commentary: Play, literacy and theories of instruction*. In K. Roskos (Ed.), *Play and literacy in early childhood research from multiple perspectives*. (pp. 133–148).
- Kenborg, L., Winther, J. F., Linnet, K. M., et al. (2018). Neurologic disorders in 4858 survivors of central nervous system tumors in childhood—An adult life after childhood Cancer in Scandinavia (ALiCCS) study. *Neuro-Oncology*, *1*(12), <https://doi.org/10.1093/neuonc/noy094>.

- Landreth, G. L. (2012). *Play therapy: The art of the relationship*. 3rd Edition. New York: Routledge.
- Lazor, T., Tigelaar, L., Pole, J. D., et al. (2017). Instruments to measure anxiety in children, adolescents, and young adults with cancer: A systematic review. *Support Care Cancer*, 25, 2921–2931. <https://doi.org/10.1007/s00520-017-3743-3>.
- Leahy, A. B., Feudtner, C., & Basch, E. (2018). Symptom monitoring in pediatric oncology using patient-reported outcomes: Why, how, and where next. *Patient*, 11, 147–153. <https://doi.org/10.1007/s40271-017-0279-z>.
- Lipstein, E. A., Lindly, O. J., Anixt, J. S., et al. (2016). Shared decision making in the care of children with developmental and behavioral disorders. *Maternal and Child Health Journal*, 20, 665–673. <https://doi.org/10.1016/j.bbi.2015.08.015>. Chronic.
- Macartney, G., Harrison, M. B., VanDenKerkhof, E., et al. (2014). Quality of life and symptoms in pediatric brain tumor survivors: A systematic review. *Journal of Pediatric Oncology Nursing*, 31, 65–77. <https://doi.org/10.1177/1043454213520191>.
- Matza, L. S., Swensen, A. R., Flood, E. M., et al. (2004). Assessment of health-related quality of life in children: A review of conceptual, methodological, and regulatory issues. *Value Health*, 7, 79–92. <https://doi.org/10.1111/j.1524-4733.2004.71273.x>.
- Medical Research Council. (2004). *Medical research involving children*. MRC Ethics Guide (p. 49).
- Meeske, K., Katz, E. R., Palmer, S. N., et al. (2004). Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer*, 101, 2116–2125. <https://doi.org/10.1002/cncr.20609>.
- Morrow, A. M., Hayen, A., Quine, S., et al. (2012). A comparison of doctors', parents' and children's reports of health states and health-related quality of life in children with chronic conditions. *Child: Care, Health and Development*, 38, 186–195. <https://doi.org/10.1111/j.1365-2214.2011.01240.x>.
- Naslund, J. A., Marsch, L. A., McHugo, G. J., et al. (2015). Emerging mHealth and eHealth interventions for serious mental illness: A review of the literature. *Journal of Mental Health*, 24, 320–331. <https://doi.org/10.3109/09638237.2015.1019054>.
- NISE Network. (2018). *Nano Around the World card game* | NISE Network. <http://www.nisenet.org/catalog/nano-around-world-card-game> (Accessed July 25, 2018).
- Park, E. S., & Cho, I. Y. (2017). Shared decision-making in the paediatric field: A literature review and concept analysis. *Scandinavian Journal of Caring Sciences*, 478–489. <https://doi.org/10.1111/scs.12496>.
- Paxton, R.J.J.L.W.R.P.M.B.M.J.L.D.-W.W. (2010). Associations between leisure-time physical activity and health-related quality of life among adolescent and adult survivors of childhood cancers. *Psychooncology*, 19, 997–1003. <https://doi.org/10.1002/pon.1654>.
- Penn, A., Shortman, R. I., Lewis, S. P., et al. (2010). Child-related determinants of health-related quality of life in children with brain tumours 1 year after diagnosis. *Pediatric Blood & Cancer*, 55, 1377–1385. <https://doi.org/10.1002/psc>.
- Phillips, S. M., Padgett, L. S., Leisenring, W. M., et al. (2015). Survivors of childhood cancer in the United States: Prevalence and burden of morbidity. *Cancer Epidemiology, Biomarkers & Prevention*, 24, 653–663. <https://doi.org/10.1158/1055-9965.EPI-14-1418>.
- Primack, B. A., Carroll, M. V., McNamara, M., et al. (2012). Role of video games in improving health-related outcomes. A systematic review. *American Journal of Preventive Medicine*, 42, 630–638. <https://doi.org/10.1016/j.amepre.2012.02.023>.
- Pui, C., Gajjar, A. J., Kane, J. R., et al. (2012). *Challenging issues in pediatric oncology*. Vol. 8. (pp. 540–549). <https://doi.org/10.1038/nrclinonc.2011.95>. Challenging.
- Quast, L. F., Phillips, P. C., Li, Y., et al. (2018). A prospective study of family predictors of health-related quality of life in pediatric brain tumor survivors. *Pediatric Blood & Cancer*, e26976. <https://doi.org/10.1002/psc.26976>.

- Rilstone, A. (1994). *Role-playing games: An overview*. *RPGnet*. <http://www.rpg.net/oracle/essays/rpgoverview.html> (Accessed July 25, 2018).
- Sato, I., Higuchi, A., Yanagisawa, T., et al. (2014). Impact of late effects on health-related quality of life in survivors of pediatric brain tumors. *Cancer Nursing*, *37*, E1–14. <https://doi.org/10.1097/NCC.000000000000110>.
- Sattoe, J. N. T., van Staa, A., & Moll, H. A. (2012). The proxy problem anatomized: Child-parent disagreement in health related quality of life reports of chronically ill adolescents. *Health and Quality of Life Outcomes*, *10*, 10. <https://doi.org/10.1186/1477-7525-10-10>.
- Schulte, F., Russell, K. B., Cullen, P., et al. (2017). Systematic review and meta-analysis of health-related quality of life in pediatric CNS tumor survivors. *Pediatric Blood & Cancer*, *64*, e26442. <https://doi.org/10.1002/pbc.26442>.
- Shook, J. R., & Giordano, J. (2014). A principled and cosmopolitan neuroethics: Considerations for international relevance. *Philosophy, Ethics, and Humanities in Medicine*, *9*, 1–13. <https://doi.org/10.1186/1747-5341-9-1>.
- Simmons, B. (2014). *The PMLD ambiguity: Articulating the life-worlds of children with profound and multiple learning disabilities* (1st ed.). London: Routledge.
- Smalley, L. P., Kenney, M. K., Denboba, D., et al. (2014). Family perceptions of shared decision-making with health care providers: Results of the national survey of children with special health care needs, 2009–2010. *Maternal and Child Health Journal*, *18*, 1316–1327. <https://doi.org/10.1007/s10995-013-1365-z>.
- Solans, M., Pane, S., Estrada, M. D., et al. (2008). Health-related quality of life measurement in children and adolescents: A systematic review of generic and disease-specific instruments. *Value Heal*, *11*, 742–764. <https://doi.org/10.1111/j.1524-4733.2007.00293.x>.
- Stiggelbout, A. M., Van Der Weijden, T., De Wit, M. P. T., et al. (2012). Shared decision making: Really putting patients at the centre of healthcare. *BMJ*, *344*, 1–6. <https://doi.org/10.1136/bmj.e256>.
- Stone, J., Waern, S., Khabra, K., et al. (2017). Impact of toxicities and neurocognitive impairment on the health related quality of life (HR-QoL) for survivors of medulloblastoma. *European Journal of Cancer*, *72*, S171. [https://doi.org/10.1016/S0959-8049\(17\)30631-7](https://doi.org/10.1016/S0959-8049(17)30631-7).
- Storm, H., Engholm, G., Mägi, M., et al. (2017). Geographical variability in survival of European children with central nervous system tumours. *European Journal of Cancer*, *82*, 137–148. <https://doi.org/10.1016/j.ejca.2017.05.028>.
- Surun, A., Dujaric, M.É., Aerts, I., et al. (2018). Enrollment in early-phase clinical trials in pediatric oncology: The experience at Institut Curie. *Pediatric Blood & Cancer*, *65*, 1–7. <https://doi.org/10.1002/pbc.26916>.
- Tabletop Role Playing Games. (2014). *Wikipedia*.
- Theunissen, N., Vogels, T., Koopman, H., et al. (2014). The proxy problem: Child report versus parent report in health-related quality of life research. *Quality of Life Research*, *7*, 387–397.
- Tock, T. I., Bhat, S., Szymonifka, J., et al. (2014). Quality of life outcomes in proton and photon treated pediatric brain tumor survivors. *Radiotherapy and Oncology*, *113*, 89–94. <https://doi.org/10.1016/j.radonc.2014.08.017>.
- Tomlinson, D., Zupanec, S., Jones, H., et al. (2016). The lived experience of fatigue in children and adolescents with cancer: A systematic review. *Support Care Cancer*, *24*, 3623–3631. <https://doi.org/10.1007/s00520-016-3253-8>.
- Vannatta, K., Gerhardt, C. A., Wells, R. J., et al. (2007). Intensity of CNS treatment for pediatric Cancer: Prediction of social outcomes in survivors. *Pediatric Blood & Cancer*, *49*, 716–722. <https://doi.org/10.1002/pbc>.

- Varni, J. W., Burwinkle, T. M., Sherman, S. A., et al. (2005). Health-related quality of life of children and adolescents with cerebral palsy: Hearing the voices of the children. *Developmental Medicine and Child Neurology*, *47*, 592–597.
- Varni, J. W., Limbers, C., & Burwinkle, T. M. (2007a). Literature review: Health-related quality of life measurement in pediatric oncology: Hearing the voices of the children. *Journal of Pediatric Psychology*, *32*, 1151–1163. <https://doi.org/10.1093/jpepsy/jsm008>.
- Varni, J. W., & Limbers, C. A. (2009). The pediatric quality of life inventory: Measuring pediatric health-related quality of life from the perspective of children and their parents. *Pediatric Clinics of North America*, *56*, 843–863. <https://doi.org/10.1016/j.pcl.2009.05.016>.
- Varni, J. W., Limbers, C. A., & Burwinkle, T. M. (2007b). Parent proxy-report of their children's health-related quality of life: An analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales. *Health and Quality of Life Outcomes*, *5*, 1–10. <https://doi.org/10.1186/1477-7525-5-2>.
- Von Rueden, U., Gosch, A., Rajmil, L., et al. (2006). Socioeconomic determinants of health related quality of life in childhood and adolescence: Results from a European study. *Journal of Epidemiology and Community Health*, *60*, 130–135. <https://doi.org/10.1136/jech.2005.039792>.
- Vygotsky, L. S. (1967). Play and its role in the mental development of the child. *Soviet Psychology*, *5*(3), 6–18. <https://doi.org/10.2753/RPO1061-040505036>.
- Wolf, S. M., Amendola, L. M., Berg, J. S., et al. (2018). Navigating the research-clinical interface in genomic medicine: Analysis from the CSER consortium. *Genetics in Medicine*, *20*, 545–553. <https://doi.org/10.1038/gim.2017.137>.
- Wolfe, J., Orellana, L., Ullrich, C., et al. (2015). Symptoms and distress in children with advanced cancer: Prospective patient-reported outcomes from the PediQUEST study. *Journal of Clinical Oncology*, *33*, 1928–1935. <https://doi.org/10.1200/JCO.2014.59.1222>.
- Wong, C., Odom, S. L., Hume, K. A., et al. (2015). Evidence-based practices for children, youth, and young adults with autism spectrum disorder: A comprehensive review. *Journal of Autism and Developmental Disorders*, *45*, 1951–1966. <https://doi.org/10.1007/s10803-014-2351-z>.