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Strategies to Improve Success of Pediatric Cancer Co-operative Group Quality of Life Studies: A Report from the Children's Oncology Group

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Abstract

Purpose—Quality of life (QoL) has been increasingly emphasized in National Cancer Institute (NCI) sponsored multi-site clinical trials. Little is known about the outcomes of these trials in pediatric cancer. Objectives were to describe the proportion of Children's Oncology Group (COG) QoL studies that successfully accrued subjects and were analyzed, presented or published.

Methods—We conducted a survey to describe outcomes of COG QoL studies. We included studies that contained at least one QoL assessment and were closed to patient accrual at the time of survey dissemination. Respondents were the investigators most responsible for the QoL aim.

Results—Sixteen studies were included; response rate was 100%. Nine (56%) studies were embedded into a cancer treatment trial. Only 3 (19%) studies accrued their intended sample size. Seven (44%) studies were analyzed, 9 (56%) were presented and 6 (38%) were published.

Conclusions—NCI-sponsored pediatric QoL studies have high rates of failure to accrue. Many were not analyzed or disseminated. Using this data, strategies have been implemented to improve conduct in future trials. Monitoring of QoL studies is important to maximize the chances of study success.

BACKGROUND

As pediatric oncology survival has increased, more attention has been placed on maximizing quality of life (QoL).[1] In general, incremental improvement in survival is diminishing with

the introduction of more intensive treatments.[2, 3] Consequently, patients, families and physicians may be faced with deciding whether small improvements in event-free survival are worthwhile. QoL may be an important factor in determining treatment-related decisions. [4]

Pediatric oncology National Cancer Institute (NCI) funded multi-institutional trials have focused on evaluating QoL in different treatment contexts. The Children's Oncology Group (COG) is the largest federally funded (NCI, USA) pediatric cancer clinical trials network worldwide and its mission is to improve the outcome for all children with cancer. COG and its legacy groups (Children's Cancer Group (CCG) and Pediatric Oncology Group (POG)) have conducted several studies of QoL. There are no published reports regarding the overall success of these QoL studies in terms of conduct or reporting.

The primary objective was to describe the proportion of COG studies that successfully accrued the target sample size or a sufficient sample size for to meet the QoL aim. Secondary objectives were to describe the proportion of studies analyzed, presented at a national or international conference, and published. An exploratory objective was to examine factors associated with accrual success.

METHODS

Identification of Studies

We focused on studies conducted by COG or its legacy groups, CCG or POG. We included studies that contained at least one QoL assessment and were closed to patient accrual at the time of survey dissemination. No other time frame for activation or closure was specified for eligibility. Studies consisted of symptom management trials in which QoL was the primary endpoint and cancer treatment trials in which QoL was a secondary endpoint QoL was defined as "physical and mental health perceptions and their correlates, including health risks and conditions, functional status, social support, and socioeconomic status".[5] Neurocognitive evaluation was not considered to be a QoL endpoint.

The list of potentially eligible studies was identified from the COG study database and NCI funding database. Four authors (PW, PC, CT and FS) reviewed instruments used in potentially eligible trials and agreed upon included instruments by consensus. All studies were approved by the Institutional Review Boards at each participating site and all subjects provided informed consent or assent as appropriate.

Survey of QoL Study Chairs

We created a survey which was pilot tested among team members and then disseminated (May 2013- August 2013). The survey asked the study chairs to confirm demographic data such as the target sample size, instruments and time points. The survey also included questions related to funding, target accrual, statistical analysis, conference presentations and publication status. COG personnel distributed the survey by email to the identified QoL chair. The QoL study chair was defined as the person from each study committee most responsible for the QoL aim. For some studies, this individual was specified in the protocol narrative. If the investigator for the QoL aim was not known, we contacted the primary

study chair to identify the QoL chair. In the event a QoL chair was not identified, then the chair for the primary cancer treatment study was surveyed. The respondent was asked to return the survey by email, mail or fax. A member of the study team (PW) contacted non-respondents by email and then by phone in the case of non-response.

Outcomes

The primary outcome was successful accrual of study subjects. We delineated two different levels of accrual success: (1) Accrual of the expected or target number; and (2) Accrual of a sufficient number of participants to meet the QoL aims as outlined in the proposal, but not the target number. Accrual failure was defined as studies that did not meet either level of accrual success. Secondary endpoints were the number of studies that were analyzed, presented at a national or international conference, and led to a peer-reviewed publication.

Statistics

The primary and secondary outcomes were descriptive. For the exploratory objective, to identify factors associated with accrual failure, we pre-specified variables of interest as follows: whether QoL was the primary aim of the study; the ability to identify the QoL study chair from the protocol; whether the population consisted of children with central nervous system tumors; studies which closed to patient accrual after 2007; and those with three or more evaluation time points. Central nervous system tumor was evaluated due to the well-described changes in QoL in these patients. The date studies were closed to patient accrual was also of interest since we anticipated older studies would be more likely to be completed compared to more recently closed studies. We also hypothesized that a large number of time points may be associated with poor accrual. In order to evaluate factors associated with failure, Fisher's exact test was used. All tests of significance were two-sided, and statistical significance was defined as $P < 0.05$. Statistical analysis was performed using the SAS statistical program (SAS-PC, version 9.3; SAS Institute Inc., Cary, NC).

RESULTS

We identified 31 potential studies. Fifteen were excluded because they did not contain a QoL endpoint, leaving 16 included studies. All surveys were completed for a response rate of 100%.

Table 1 illustrates the characteristics of the 16 identified studies; details are contained in Appendix 1. The most common underlying cancer types were central nervous system tumors ($n=5$), acute lymphoblastic leukemia ($n=3$) and solid tumors ($n=4$). The majority of studies ($n=9$) were embedded into a cancer treatment study. The QoL aim was the primary aim in 7 (44%) studies.

The majority of studies provided financial support to the institutions for accrual, with the majority of support coming from the NCI (9/16, 56%). No funding for patient accrual was available for 5 (31%) studies. The QoL data was in the possession of the QoL study chair in 7 studies (44%), at CCG/POG/COG in 6 (38%), unknown in 2 (13%) (study chair could not identify the current location of the data), and other in 1 study (6%).

Table 2 illustrates the success outcomes. Only 3 (19%) studies accrued their intended sample size for the QoL aim. Seven (44%) studies were analyzed, 9 (56%) were presented and 6 (38%) were published in the peer-reviewed literature.

Table 3 describes factors associated with accrual failure. The ability to identify the QoL study chair in the protocol was significantly associated with accrual success (89% vs 29%; $P=0.035$). Studies in which the QoL aim was the primary aim and those with less than 3 assessment time points had higher accrual success rates, although these analyses did not achieve statistical significance.

DISCUSSION

We have demonstrated that among NCI-sponsored COG clinical trials, QoL studies have high rates of failure to accrue. Further, most studies were never analyzed and most were not published in the peer-reviewed literature, even though half of these studies closed to patient accrual over 7 years ago. It is important to note that the vast majority of COG studies do not include a QoL assessment since only 16 studies were identified.

Challenges with the conduct of supportive care studies have been well described.[6–11] Reasons for failure to accrue to these studies include lack of prioritization, consent fatigue, institutional burden, lack of financial incentives, and lack of an institutional advocate or champion.[6, 7, 10, 11]

Factors which may be important to accrual success rates were the ability to identify the QoL chair in the protocol narrative, the QoL aim being the primary objective and having fewer QoL assessment time points. Based on these results, COG now ensures there is an identified individual responsible for the QoL aim and minimizes the number of QoL assessment time points. We do not require that the QoL aim is the primary objective since we believe embedded trials have value since they are efficient and allow correlation between QoL and survival outcomes. It is also notable that study data could not be located for 2 studies; COG also has created policies around QoL data storage.

The strength of this report is the 100% response rate and the ability to conduct this study at the federally funded multi-site level. There are several limitations to this study. We included all studies closed to patient accrual and 4 are still assessing QoL in late time points. However, 50% of studies were closed during or prior to 2007; all of these studies have completed even late QoL time points. Second, other pediatric and adult multi-center clinical trial groups may have very different results than ours, particularly if they face different barriers and obstacles and thus, results are only generalizable to the COG context. Finally, the sample size was very small.

In conclusion, NCI-sponsored pediatric QoL studies have high rates of failure to accrue. Many were not analyzed or disseminated. Using this data, strategies have been implemented to improve conduct in future trials. We suggest that policies be in place to ensure dissemination of findings for those studies that do achieve adequate accrual.

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Appendix 1. Details of included studies

Cancer Type	QoL Primary Aim	QoL Instruments	Number of Time Points	Respondent Type	Year Study Closed
Lymphoma	Yes	CCSS Baseline Questionnaire	1	Self OR proxy	2011
ALL	No	PedsQL	2	Self and proxy OR self	2011
Solid tumor	No	EORTC QLQ-C30; PedsQL	4	Self and proxy OR self	2011
CNS	No	PedsQL; PedsQL Cancer	3	Self and proxy OR self	2011

Cancer Type	QoL Primary Aim	QoL Instruments	Number of Time Points	Respondent Type	Year Study Closed
ALL	No	PedsQL; PedsQL Cancer	5	Self and proxy	2010
CNS	No	PedQL; SF-36	3	Self and proxy OR self	2009
Solid tumor	No	EORTC QLQ-C30; PCQL	5	Self	2009
ALL	Yes	PedsQL	1	Self and proxy	2008
CNS	No	PCQL-32	3	Self and proxy	2007
Solid tumor	Yes	PedsQL	1	Self and proxy	2005
AML	Yes	CCSS Baseline Questionnaire; SF-36; CHQ	1	Self and proxy OR self	2005
HSCT	No	PedsQL; PedsQL Cancer; FACT-BMT	3	Self and proxy OR self	2005
CNS	Yes	CHQ; SF-36	1	Self and proxy OR self	2005
CNS	No	NIH IPI	5	Self and proxy	2003
Other	Yes	MM-QOL; CHQ	1	self	2002
Other	Yes	CHQ; SF-36	3	Self and proxy OR self	2001

Abbreviation: QoL - quality of life; CCSS Baseline Questionnaire - Childhood Cancer Survivor Study Baseline Questionnaire; PedsQL - Pediatric Quality of Life Inventory; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 36; PCQL - Pediatric Cancer Quality of Life Inventory; CHQ - Child Health Questionnaire; FACT-BMT - Functional Assessment of Cancer Therapy, Bone Marrow Transplantation; NIH IPI-; National Institute of Health Impact of Pediatric Illness; MM-QOL - Minneapolis-Manchester Quality of Life

** Age-dependent where older patients only completed self-report while younger patients had proxy-report and self-report

TABLE 1

Demographics of included studies of quality of life in Children's Oncology Group Trials (N=16)

Characteristics	n (%)
Cancer Type	
Central nervous system	5 (31%)
Solid tumors	4 (25%)
Acute lymphoblastic leukemia	3 (19%)
Multiple diagnoses	2 (13%)
Other	2 (13%)
Quality of Life was Primary Aim of Study	7 (44%)
Able to Identify QoL Study Chair in Protocol	10 (63%)
Specific Instrument**	
PedsQL v 4.0 Generic Core Scales	8 (29%)
SF-36	4 (25%)
Other	6 (38%)
Number of Assessment Time Points	
3 or more	9 (56%)
Instrument Respondent Type	
Self and proxy-report OR self-report*	8 (62%)
Self and proxy-report	5 (31%)
Self or proxy-report	1 (6%)
Only self-report	2 (13%)
Year Study Closed	
After 2007	8 (50%)

Abbreviation: QoL - quality of life; PedsQL- Pediatric Quality of Life Inventory

* Age-dependent where older patients only completed self-report while younger patients had proxy-report and self-report

** Some studies had more than one instrument

TABLE 2

Success of Children's Oncology Group Quality of Life Studies (N=16)

Outcomes	n (%)
Accrual	
Expected or target number	3 (19%)
Sufficient to meet QoL study aim	6 (38%)
Failure	7 (44%)
Statistical Analysis Completed	7 (44%)
Presented at Conference	9 (56%)
Published in Peer-Reviewed Literature	6 (38%)

TABLE 3

Factors associated with failure to accrual sufficient subjects to meet the quality of life aim as outlined in the Proposal

Outcomes and Factors	Success [*] N=9	Failure N=7	P value ^{**}
QoL Primary Aim	6 (67%)	1 (14%)	0.060
Able to Identify QoL Study Chair	8 (89%)	2 (29%)	0.035
Population CNS Tumors	2 (22%)	3 (43%)	0.596
Year Study Closed > 2007	5 (56%)	3 (43%)	1.000
Number of Time Points 3	3 (33%)	6 (86%)	0.060

Abbreviation: QoL - quality of life; CNS - central nervous system

* Success was defined as accrual of the expected or target sample size (n=3) or accrual of a sufficient number of participants to meet the QoL aims as outlined in the proposal, but not the target number (n=6)

** Using Fisher's exact test