Quality of patient-reported outcome reporting according to the CONSORT statement in randomized controlled trials with glioblastoma patients

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Abstract

Background. Randomized controlled trials (RCTs) represent the best evidence in oncology research. Glioblastoma is the most frequent and deadly primary brain tumor, affecting health-related quality of life. An important end point is patient-reported outcomes (PROs). There are no data regarding how well publications of glioblastoma RCTs report PROs. A specific PRO extension of the Consolidated Standards of Reporting Trials (CONSORT) statement was created to improve the quality of reporting. The aim of this study was to evaluate adherence to the CONSORT-PRO statement in reporting RCTs addressing the treatment of patients with glioblastoma. PRO analysis methodology was explored and criteria associated with higher quality of reporting were investigated.

Methods. From PubMed/MEDLINE and the Cochrane Library databases, all phase 2 and 3 RCTs related to glioblastoma published between 1995 and 2018 were reviewed according to the CONSORT-PRO statements. An overall quality score on a 0 to 100 scale was defined based on these criteria and factors associated with this score were identified.

Results. Forty-four RCTs were identified as relevant according to predefined criteria. The median overall quality score was 26. No difference was observed regarding reporting quality over the years. CONSORT-PRO items concerning data collection and analysis were poorly reported. Thirty-four trials (77%) used longitudinal data. The most frequent statistical method for PROs analysis was the mean change from baseline (63%). Factors associated with improved overall quality score were the presence of a secondary publication dedicated to PROs results, the statement of any targeted dimensions, and when trials reported results using multiple methods.

Conclusion. Despite the importance of measuring PROs in patients with glioblastoma, employment of the CONSORT-PRO statement is poor in RCTs.

Keywords

CONSORT-PRO statement | glioblastoma | health-related quality of life | patient-reported outcomes | randomized controlled trials

Glioblastoma multiforme is the most common high-grade glioma according to the World Health Organization classification¹ and the second-most frequent CNS tumor after meningioma.² It remains an incurable disease with a dismal prognosis. Median overall survival is low: 15 months for newly diagnosed glioblastoma and 5 to 7 months for recurrent/relapsed glioblastoma; 5-year survival is about 5%.³ Owing to disease progression, patients with glioblastoma experience a progressive decline in neurologic function and health-related quality of life (HRQoL). The current standard of care for patients with newly diagnosed glioblastoma comprises maximum feasible surgical resection followed by radiotherapy with concomitant and maintenance therapy with temozolomide.^{4–6} Since 2005,^{7,8} no new standard of care has demonstrated a significant benefit neither in term of overall survival nor HRQoL. The tumor-treating field device represents an additional treatment option for glioblastoma, with an extended survival to 20.9 months,⁹ and has been approved by the US FDA. Treatment at recurrence, including second surgery, reirradiation, antiangiogenic therapy using bevacizumab, or chemotherapy (eg, lomustine, temozolomide rechallenge, other alkylating agent), has not shown any significant improvement in terms of survival in a randomized trial. Data on immunotherapy and new targeted-therapies are still needed. Long-term survival studies describe significantly impaired cognition and reduced HRQoL in patients with glioblastoma.^{10–12} Therefore, before a therapy decision, it is important to weigh the balance between a potential treatment benefit and the impact on the patient's HRQoL. Concerns for patients with glioblastoma are to reduce morbidity, and to preserve and improve neurologic functions and capacity to perform daily activities as long as possible and functional independence.^{13,14}

Randomized controlled trials (RCTs), in neuro-oncology, similarly to other areas of medicine, remain the gold standard for evidence-based practice and approval for new therapies.^{15,16} Physicians usually judge the importance of RCTs based on the quality of published reports. Additionally, the quality of reporting is fundamental for guiding peer-review decisions, for experts' guidelines, and to conduct unbiased meta-analysis, which is essential in neuro-oncology because many individual RCTs are underpowered to detect small effect sizes. To improve the quality of reporting of RCTs, the Consolidated Standards of Reporting Trials (CONSORT) statement was developed.^{17–19} These recommendations comprise a checklist and flow diagram that can be used to report an RCT. It is now endorsed by almost all biomedical journals, and its use has been associated with improved reporting of oncology trials.^{20–26}

Patient-reported outcomes (PROs) including HRQoL, symptoms, and satisfaction with care, are measures reported by patients themselves. The FDA considers HRQoL an end point in assessing clinical benefit, offering 2 advantages in oncology clinical trials: a propensity to assess clinical patient benefit and reduced study duration.²⁷ RCTs have gradually incorporated HRQoL or other types of PROs as end points.²⁸ The inclusion of PROs in new treatment development has great potential for adding invaluable information for better understanding the efficiency of novel drugs.²⁹ However, collecting PROs in RCTs has specific challenges.^{30,31} To enhance

the consistency of PRO reporting in RCTs, the CONSORT-PRO extension was developed in 2013.³² It adds 5 PRO-specific extension statements and brings PRO-specific explanations to 9 CONSORT items. Despite recent global progress and interest in the field of HRQoL outcomes for patients with cancer, improvements are lacking for patients with glioblastoma.¹² We assumed this could be associated, at least in part, with the quality of reporting.

The aim of this study was to assess the implementation of the specific CONSORT-PRO criteria in reporting on RCTs addressing the treatment of glioblastomas in adult patients. We also aimed at determining criteria associated with better reporting quality.

Methods

Trial Selection

We conducted a search on PubMed/MEDLINE, the Cochrane Library databases, and through manual searching to identify all published RCTs in the field of glioblastoma between January 1995 and November 2018. The search was performed using the terms “glioblastoma,” “randomized controlled trials,” and “humans” as key words (algorithm described in [Supplement 1](#)). All phase 2 and 3 RCTs published in English on any type of treatment and glioblastoma were included. They had to include PROs analyses. A trial was defined as an RCT if a control group was present and if the assignment of participants to intervention was specified as “randomized,” “randomly allocated,” “assigned at random,” or “allocated by randomization.” We excluded pediatric trials and trials without glioblastoma patients. Review articles and meta-analyses were not considered. When the same trial was published more than once, we kept the report based on the primary outcome of the article with the most updated results. In case of a subordinate report specifically on PROs, published secondarily or as a companion paper to the primary report, we retained the article with the most PROs data available. Two reviewers independently assessed the eligibility of all identified articles. Articles that did not meet the inclusion criteria when screening the titles and abstracts or the full paper were excluded. We reported the exclusion reasons for ineligible articles. Any disagreement between readers was resolved by consensus and/or by another reviewer.

Data Acquisition and Development of Overall Quality Score

For each selected article, a data collection form was created to extract 19 relevant items of the CONSORT-PRO statement ([Table 2](#)). Two reviewers independently scored each item. The items were evaluated and rated as “correctly reported” (scored as 2 points), “unclear” (scored as 1 point), or “not reported” (scored as 0 point). Thereby, an overall quality score (OQS) ranging from 0 to 38 was created and standardized on a 0 to 100 scale for each trial to qualify the quality of reporting (the higher the score, the higher the quality).

Additional data regarding trials characteristics were collected: date of publication; number of enrolled patients; inclusion period date; period of intervention (postsurgery,

subsequent lines of treatment, or others); international study and center information; phase 2 or 3; presence of an industrial funding; journal in which the article was published; and its impact factor. We also extracted data regarding the use of performance scales for the selection of patients: KPS and the Eastern Cooperative Oncology Group Performance Status (ECOG PS). We searched for the positivity of the trial as the primary outcome. In addition, we collected information about PRO assessment: PRO end point status, PRO population considered for the analyses, questionnaire(s) used, exact PRO assessments, and presentation of results. We gathered information about PRO analyses: statement of any targeted dimension(s) representing a focus on interesting dimensions of a questionnaire, statement of the considered minimal clinically important difference (MCID) representing the smallest change in an outcome that a patient would identify as important,³³ and statement of longitudinal data and method used for analyses.

Statistical Analysis

We conducted a descriptive analysis of selected publications. Characteristics of trials were described using absolute and relative frequencies. Analyses were carried out by comparing 2 groups: publications between 1995 and 2013 vs 2014 and 2018, using the χ^2 or Fisher exact test. For each trial, the OQS was the sum of the score of the 19 relevant items. Trials in which items were “correctly reported” and agreement between judges were described by absolute, relative frequencies and 95% CI. Univariate analysis using Mann-Whitney or Kruskal-Wallis nonparametric tests was used to identify factors associated with OQS, including all the previously mentioned covariates. The statistical significance was set as 5% and tests were 2-sided. Analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc).

Results

Study Selection Process

Of the 2930 references initially retrieved, 2459 articles were screened after removing duplicates. One article was retrieved from manual searching (Figure 1). After reading titles and abstracts, 2259 trials were excluded. A total of 201 articles (8%) were then selected for a complete reading. Most of them did not have PROs data ($n = 95$) and were excluded. Finally, a total of 44 relevant RCTs (2%), published between 1995 and 2018, were included in the final analysis according to our predefined inclusion criteria (Supplement 2).

Characteristics of Selected Randomized Controlled Trials

The characteristics of RCTs included in the final analysis are described in Table 1. The RCTs were published predominantly in 4 journals, namely *Journal of Clinical Oncology* ($n = 9$, 21%), *Neuro-Oncology* ($n = 6$, 14%), *New England*

Journal of Medicine ($n = 4$, 9%), and *Lancet Oncology* ($n = 4$, 9%). The primary end points of the studies were mainly overall survival ($n = 22$, 50%) and progression-free survival ($n = 12$, 27%). Statistically significant results in favor of the investigational arm were observed in 10 trials (23%). Half of the RTCs were international and phase 3 trials ($n = 22$, 50%). Most of them were supported by industry ($n = 34$, 77%) and were multicentric ($n = 40$, 91%). Twenty-three (52%) and 18 RCTs (41%) aimed at assessing postsurgery protocols and subsequent treatments, respectively. Three RCTs (7%) focused on patients who underwent radiotherapy regardless of the line of treatment. In addition to glioblastoma histology, a minimum KPS was an inclusion criteria for 27 trials (61%) and good ECOG PS for 17 trials (39%). A total of 10 844 patients were randomly assigned and baseline PROs sample were available for 8210 patients (76%). The difference came from 7 trials (16%) in which PRO samples were not mentioned. In 3 trials (7%), the number of PRO data available matched the number of patients randomly assigned during the trial (data not shown).

Methods of Patient-reported Outcome Reporting

Eleven RCTs (25%) published results of PRO data in a dedicated manuscript. PROs were mostly considered as a secondary end point ($n = 34$, 77%), whereas 2 trials (5%) considered PROs as the primary end point. Thirty-seven trials (84%) specified the first assessment to be before the treatment (eg, “baseline,” “at randomization,” “before study treatment,” “on the first day of the treatment”). Three articles (7%) did not provide any time lapse for evaluation, and 4 (9%) did not specify a baseline assessment. Assessment after the end of treatment was specified in only 12 trials (27%). A schedule for assessments during treatment was provided in 41 manuscripts (93%). Taken together, 12 trials (27%) provided at least 3 HRQoL assessments (at baseline, during treatment, and at the end of the study) (data not shown). The population used for the analyses of longitudinal PROs data was defined as intention-to-treat in 6 trials (14%) and modified intention-to-treat in 8 trials (18%). It was not clearly defined in 11 studies (25%) and not reported at all in 19 trials (43%). To measure HRQoL, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 was the most frequently used instrument ($n = 30$, 68%). The brain-cancer specific module EORTC QLQ-BN20 was added to the QLQ-C30 in 26 studies (59%). The palliative-specific questionnaire EORTC QLQ-C15-PAL, in association with the QLQ-BN20, was used in 1 study (2%). The Functional Assessment of Cancer Therapy (FACT) questionnaires were used in 11 studies (25%): 1 study (2%) used the FACT-General Version, 7 studies (16%) used the FACT-Brain, and 3 studies (7%) used the FACT-Fatigue questionnaire. Ten trials used alternative questionnaires, and one study did not specify the PRO questionnaire used (see Table 1).

The targeted dimensions were prespecified in 15 studies (34%) in “Methods.” Longitudinal data were used to compare PROs between treatment arms in 34 trials (77%). Among analyses performed for longitudinal PROs data, the mean

Figure 1. Flow Diagram of Systematic Review of Randomized Controlled Trials Article Selection (According to PRISMA Statement) *One article included 2 trials. PRISMA, Preferred Reporting Items for Systematic Review and Meta-analyses; PRO, patient-reported outcomes.

change from baseline was predominantly used ($n = 14$, 41%), followed by general linear mixed model (LMM) ($n = 12$, 35%) and time to deterioration (TTD) analysis ($n = 10$, 29%). Seventeen studies (39%) defined the MCID, which was a 10-point decrease in the global HRQoL scores for those who used 1 of the 3 EORTC questionnaires. Reporting of the results was heterogeneous: Eight trials (18%) presented them only by text in the core of the manuscript, 8 (18%) and 15 trials (34%) added graphics or tables, respectively, and 12 trials (27%) presented results with the 3 types. One trial (2%) mentioned PRO analyses and did not report any result.

Consolidated Standards of Reporting Trials Score Rating and Overall Quality Score

The median percentage of agreement between judges was 77.3% (range, 61.4%-97.7%) for the 19 evaluated items constituting the OQS (see Table 2). The median OQS was

26 (range, 3-81). Two trials (5%) did not report any item correctly. No manuscript reported correctly all the 5 PRO-specific extensions of the CONSORT statement (ie, P1b, P2b, P6a, P12a, and P20/21). The most frequently correctly reported item was the description of the number of PRO data available at baseline (reported in 55% RCTs). The description of the number of PRO data available at subsequent time points was correctly reported in only 43% of RCTs. The identification of the PROs in the abstract as a primary or secondary end point, when it was not an exploratory analysis, was correctly reported in 28% of the trials. Statement of the PRO hypothesis and identification of its relevant domains, when PRO reporting was not exploratory, were found in 10% and 3% of the manuscripts, respectively. The evidence of PRO instrument validity was reported in 20 trials (46%). Also, only 16 (36%) and 3 (7%) studies referred to who completed the questionnaires and the method of completion (ie, paper, telephone,

Table 1. Characteristics of Included Glioblastoma Randomized Clinical Trials

	All (n = 44)		1995-2013 (n = 22)		2014-2018 (n = 22)		P
	n	%	n	%	n	%	
Name of journal							-
<i>Journal of Clinical Oncology</i>	9	20.5	7	31.8	2	9.1	
<i>Clinical Cancer Research</i>	2	4.6	0	0.0	2	9.1	
<i>Journal of Neuro-Oncology</i>	3	6.8	2	9.1	1	4.6	
<i>Neuro-Oncology</i>	6	13.6	1	4.6	5	22.7	
<i>International Journal of Radiation Oncology, Biology, Physics</i>	3	6.8	3	13.6	0	0.0	
<i>New England Journal of Medicine</i>	4	9.1	1	4.6	3	13.6	
<i>Lancet Oncology</i>	4	9.1	3	13.6	1	4.6	
<i>Journal of the American Medical Association</i>	1	2.3	0	0.0	1	4.6	
<i>Annals of Oncology</i>	1	2.3	0	0.0	1	4.6	
<i>European Journal of Cancer</i>	3	6.8	1	4.6	2	9.1	
<i>British Journal of Cancer</i>	1	2.3	1	4.6	0	0.0	
<i>Journal of Neurosurgery</i>	1	2.3	1	4.6	0	0.0	
<i>Neuro-Oncology Practice</i>	1	2.3	0	0.0	1	4.6	
<i>Oncotarget</i>	1	2.3	0	0.0	1	4.6	
<i>PloS One</i>	1	2.3	0	0.0	1	4.6	
<i>Radiotherapy and Oncology</i>	1	2.3	1	4.6	0	0.0	
<i>Strahlentherapie und Onkologie</i>	1	2.3	1	4.6	0	0.0	
<i>The Oncologist</i>	1	2.3	0	0.0	1	4.6	
Publication status							.728
Main publication	33	75.0	17	77.3	16	72.7	
Secondary publication dedicated to PRO results	11	25.0	5	22.7	6	27.3	
International trial							.437 ^a
Yes	22	50.0	11	50.0	11	50.0	
No	20	45.5	9	40.9	11	50.0	
Not specified	2	4.5	2	9.1	0	0.0	
Industry supported							.011 ^a
Yes	34	77.3	13	59.1	21	95.5	
No	8	18.2	7	31.8	1	4.5	
Not specified	2	4.6	2	9.1	0	0.0	
Multicenter trial							.108 ^a
Yes	40	90.9	18	81.8	22	100.0	
No	1	2.3	1	4.6	0	0.0	
Not specified	3	6.8	3	13.6	0	0.0	
Trial phase							.048 ^a
2	18	40.9	6	27.3	12	54.6	
3	22	50.0	12	54.6	10	45.5	
Unclear/Not specified	4	9.1	4	18.2	0	0.0	
Treatment line							.267 ^a
Postsurgery	23	52.3	13	59.1	10	45.5	
Subsequent treatment	18	40.9	9	40.9	9	40.9	
Patients underwent radiotherapy	3	6.8	0	0.0	3	13.6	
Inclusion criteria							.353
KPS	27	61.4	15	68.2	12	54.6	
ECOG performance status	17	38.6	7	31.8	10	45.5	

Table 1. Continued

	All (n = 44)		1995-2013 (n = 22)		2014-2018 (n = 22)		P
	n	%	n	%	n	%	
Primary end point							.310 ^a
OS	22	50.0	13	59.1	9	40.9	
PFS	12	27.3	5	22.7	7	31.8	
OS and PFS	3	6.8	1	4.6	2	9.1	
Other ^b	5	11.4	1	4.6	4	18.2	
Not specified	2	4.6	2	9.1	0	0.0	
Positivity of primary end point							.524 ^a
Yes	10	22.7	5	22.7	5	22.7	
No	28	63.6	15	68.2	13	59.1	
Not applicable	5	11.4	1	4.6	4	18.2	
Not specified	1	2.3	1	4.6	0	0	
PRO end point							.325 ^a
Primary	2	4.5	0	0.0	2	9.1	
Secondary	34	77.3	18	81.8	16	72.7	
Exploratory	4	9.1	1	4.6	3	13.6	
Not reported	4	9.1	3	13.6	1	4.6	
PRO population							.438 ^a
Intention-to-treat	6	13.6	3	13.6	3	13.6	
Modified intention-to-treat	8	18.2	2	9.1	6	27.3	
Unclear	11	25.0	7	31.8	4	18.2	
Not reported	19	43.2	10	45.5	9	40.9	
PRO questionnaires							—
QLQ-C30	30	68.2	13	59.1	17	77.3	
QLQ-BN20	27	61.4	11	50.0	16	72.7	
QLQ-C15-PAL	1	2.3	0	0.0	1	4.5	
FACT-Br	7	15.9	5	22.7	2	9.1	
FACT-F	3	6.8	0	0.0	3	13.6	
FACT-G	1	2.3	0	0.0	1	4.5	
Brief Fatigue Inventory	2	4.5	0	0.0	2	9.1	
Brief Neurological Function	1	2.3	1	4.5	0	0.0	
Cancer Fatigue Scale	1	2.3	0	0.0	1	4.5	
MD Anderson Symptom Inventory–Brain Tumor	4	9.1	1	4.5	3	13.6	
Spitzer Quality of Life Index	1	2.3	1	4.5	0	0.0	
The Toronto Instrument	1	2.3	1	4.5	0	0.0	
Unclear	1	2.3	1	4.5	0	0.0	
Targeted dimensions							1.000 ^a
Yes	15	34.1	7	31.8	8	36.4	
No	28	63.6	14	63.6	14	63.6	
Unclear	1	2.3	1	4.6	0	0.0	
Longitudinal data							1.000 ^a
Yes	34	77.3	17	77.3	17	77.3	
No	4	9.1	2	9.1	2	9.1	
Unclear/Not specified	6	13.6	3	13.6	3	13.6	
Analysis performed for longitudinal PROs data (n = 34)							—
Time to deterioration	10	29.4	2	11.8	8	47.1	

Table 1. Continued

	All (n = 44)		1995-2013 (n = 22)		2014-2018 (n = 22)		P
	n	%	n	%	n	%	
General linear mixed model	12	35.3	3	17.6	9	52.9	
Generalized estimating equation	1	2.9	0	0.0	1	5.9	
Pattern mixture model	2	5.9	1	5.9	1	5.9	
Summary statistics	22	64.7	11	64.7	11	64.7	
Analysis of variance	1	2.9	1	5.9	0	0.0	
Regression model	1	2.9	0	0.0	1	5.9	
Repeated measure	1	2.9	1	5.9	0	0.0	
Summary statistics (n = 22)							—
Mean	2	9.1	0	0.0	2	18.2	
Mean change from baseline	14	63.6	6	54.5	8	72.7	
Mean duration of response	2	9.1	2	18.2	0	0.0	
Median change from baseline	3	13.6	1	9.1	2	18.2	
Categorical response	8	36.4	3	27.3	5	45.5	
Unclear	1	4.5	1	9.1	0	0.0	
Minimal clinically important difference defined (n = 34)							.732
Yes	17	50.0	8	47.1	9	52.9	
No	17	50.0	9	52.9	8	47.1	
Reporting of results							.810 ^a
Texts only	8	18.2	3	13.6	5	22.7	
Texts and graphics	8	18.2	5	22.7	3	13.6	
Texts and tables	15	34.1	7	31.8	8	36.4	
Texts, graphics, and tables	12	27.3	6	27.3	6	27.3	
None	1	2.3	1	4.6	0	0.0	

Percentages greater than 100 are possible because several possible responses could be considered per study. A χ^2 test is used unless indicated otherwise.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FACT-Br, Functional Assessment of Cancer Therapy–Brain; FACT-F, Functional Assessment of Cancer Therapy–Fatigue; FACT-G, Functional Assessment of Cancer Therapy–General Version; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; QLQ, quality of life questionnaire.

^aFisher exact test.

^bTime to treatment failure, time to progression, difference in 42-day change in FACT-F, reduction of fatigue, or overall cognitive performance.

electronic, or other), respectively. Statistical approaches for managing missing data were described in only 6 RCTs (14%). Proper description of each domain result for multidimensional PROs was found in less than 30% of trials. In “Discussion” sections, the trial limitations and generalizability issues were discussed in 32% and 27% of trials, respectively; clinical significance of the PROs findings was discussed in 46% of trials.

Factors Associated With Better Reporting Quality

Secondary publications dedicated to PROs results had a statistically higher OQS compared to main publications (median OQS 63 [44–81] vs 22 [3–72]; $P < .001$) (Table 3). Quality of reporting was not affected by the period of

publication, according to the 2013 CONSORT-PRO statement (median OQS = 25 during the 1995-2013 period vs median OQS = 26 during the 2014-2018 period; $P = .591$). Trial and journal characteristics were not associated with OQS (see Table 3). The use of prespecified targeted dimensions was associated with median OQS ($P = .015$). Subsequently, trials that reported results using texts, graphics, and tables had a significantly higher OQS ($P < .001$).

Discussion

In daily practice, PROs are useful to guide treatment decisions, focus on patient health goals, and support shared decision making.³⁴ Nowadays, many clinicians are still unfamiliar with PROs management, and collecting data

Table 2. Overall quality of reporting rating using items from 2013 CONSORT-PRO extension items

Item No.	Description of CONSORT-PRO criteria	No. of trials in which item was correctly reported		No. of trials in which judges were concordant (before disagreement solved)		
		n	% (95% CI)	n	% (95% CI)	
Title and abstract						
P1b ^a	Identification of PROs in abstract as primary or secondary outcome	11	27.5 (14.6-43.9)	31	70.5 (54.8-83.2)	
Introduction						
2a	Background and rationale for PROs assessment	14	31.8 (18.6-47.6)	37	84.1 (69.9-93.4)	
P2bi ^a	Statement of PROs hypothesis	4	10.0 (2.8-23.7)	30	68.2 (52.4-81.4)	
P2bii ^a	Identification of PROs relevant domains	1	2.5 (0.0-13.2)	34	77.3 (62.2-88.5)	
Methods						
4a ^a	PROs used in eligibility criteria or stratification criteria	1	100.0 (2.5-100.0)	43	97.7 (88.0-100.0)	
P6ai	Evidence of PRO instrument validity and reliability	20	45.5 (30.4-61.2)	36	81.8 (67.3-91.8)	
P6aii	Statement of person completing PROs	16	36.4 (22.4-52.2)	34	77.3 (62.2-88.5)	
P6aiii	Methods of data collection (paper, telephone, electronic, other)	3	6.8 (1.4-18.7)	41	93.2 (81.3-98.6)	
7a ^a	How sample size was determined (not required unless PRO is primary end point)	2	100.0 (15.8-100.0)	43	97.7 (88.0-100.0)	
Randomization						
P12a	Statistical approaches for dealing with missing data are explicitly stated	6	13.6 (5.2-27.4)	34	77.3 (62.2-88.5)	
Results						
13ai	Description of number of PRO outcome data at baseline	24	54.6 (38.9-69.6)	31	70.5 (54.8-83.2)	
P13aii	Description of number of PRO outcome data at subsequent time points	19	43.2 (28.4-59.9)	28	63.6 (47.8-77.6)	
15	Table showing baseline PRO data	16	36.4 (22.4-52.2)	28	63.6 (47.8-77.6)	
16	Number of patients included in each PRO analysis	17	38.6 (24.4-54.5)	27	61.4 (45.5-75.6)	
17a	For each targeted domain, results for each group, estimated effect size, and its precision (eg, 95% CI)	13	29.6 (16.8-45.2)	29	65.9 (50.1-79.5)	
18 ^a	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	4	100.0 (39.8-100.0)	30	68.2 (52.4-81.4)	
Discussion						
P20	Limitations of PRO components explicitly discussed	14	31.8 (18.6-47.6)	35	79.5 (64.7-90.2)	
P21	Generalizability issues related to PRO results should be discussed	12	27.3 (15.0-42.8)	35	79.5 (64.7-90.2)	
22	Clinical significance of PRO findings should be discussed	20	45.5 (30.4-61.2)	32	72.7 (57.2-85.0)	

PRO-specific extension statements are prefaced by the letter P.

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; PROs, patient-reported outcomes.

^aPercentages calculated only among trials for which the item was applicable.

has to be done according to strict protocols to avoid uncertainties and fluctuations in clinical practice.^{35,36} HRQoL is reduced in patients with glioblastoma.^{11,12} Treatments are meant to prolonged overall survival and progression-free survival and should therefore maintain or increase HRQoL.^{14,37} To our knowledge, this is the first systemic

evaluation of the quality of reporting of RCTs according to the CONSORT-PRO extension statement focusing specifically on glioblastoma. This study showed that OQS of trials was low; meaning the quality of PROs reporting between 1995 and 2018 was poor. With the introduction of the CONSORT statement,¹⁷⁻¹⁹ the quality of reporting of RCTs

Table 3. Univariate analysis of factors associated with CONSORT-PRO score

	n (%)	Median OQS (range)	P ^a
Publication year			.591
1995-2013	22 (50.0)	25 (3-76)	
2014-2018	22 (50.0)	26 (3-81)	
Publication status			< .001
Main publication	33 (75.0)	22 (3-72)	
Secondary publication dedicated to PRO results	11 (25.0)	63 (44-81)	
Impact factor of main publication			.120
< 10	23 (56.1)	22 (3-81)	
10-20	7 (17.1)	31 (9-76)	
> 20	11 (26.8)	31 (6-81)	
International trial			.328
Yes	22 (50.0)	22 (3-81)	
No	20 (45.5)	31 (3-81)	
Not specified	2 (4.5)	53 (53-53)	
Industry supported			.900
Yes	34 (77.3)	28 (3-81)	
No	8 (18.2)	33 (6-63)	
Not specified	2 (4.6)	22 (22-22)	
Multicenter trial			.437
Yes	40 (90.9)	24 (3-81)	
No	1 (2.3)	22 (22-22)	
Not specified	3 (6.8)	53 (44-53)	
Trial phase			.570
2	18 (40.9)	20 (3-81)	
3	22 (50.0)	31 (6-81)	
Unclear/Not specified	4 (9.1)	33 (6-44)	
Treatment line			.069
Postsurgery	23 (52.3)	28 (6-81)	
Subsequent treatment	18 (40.9)	20 (3-81)	
Patients underwent radiotherapy	3 (6.8)	58 (56-72)	
PRO end point			.162
Primary	2 (4.5)	65 (58-72)	
Secondary	34 (77.3)	22 (3-81)	
Exploratory	4 (9.1)	29 (23-54)	
Not reported	4 (9.1)	48 (25-53)	
PRO population			.070
Intention-to-treat/Modified intention-to-treat	14 (31.8)	44 (3-81)	
Unclear/Not reported	30 (68.2)	22 (3-81)	
Targeted dimensions			.015
Yes	15 (34.1)	53 (6-81)	
No	28 (63.6)	22 (3-72)	
Unclear	1 (2.3)	13 (13-13)	
Longitudinal data			.113

Table 3. Continued

	n (%)	Median OQS (range)	P ^a
Yes	34 (77.3)	29 (3-81)	
No	4 (9.1)	19 (6-44)	
Unclear/Not specified	6 (13.6)	13 (6-44)	
Reporting of results			< .001
Text only	8 (18.2)	6 (3-31)	
Texts and graphics or tables	23 (52.3)	20 (6-72)	
Texts, graphics, and tables	12 (27.3)	63 (9-81)	
None	1 (2.3)	6 (6-6)	

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; OQS: overall quality score; PRO, patient-reported outcomes.
^aMann-Whitney or Kruskal-Wallis nonparametric tests were used.

has improved in the field of oncology.²¹⁻²⁴ Regarding PROs, however, the quality of reporting of RCTs remained low over the years, even with the standardization of reporting with the extension in 2013 of the CONSORT-PRO.³⁸⁻⁴¹

Two recent analyses of RCTs in oncology with a PRO component showed that adherence to the CONSORT-PRO extension is insufficient.^{38,39} One of our results indicated that the only factor associated with improved PRO reporting was the presence of a supplementary PRO report. These studies represented all types of tumors without a focus on brain tumors. A more recent study, not specific to oncology trials, noted improvement in PRO reporting associated with journal endorsement and author use of the CONSORT-PRO extension.⁴⁰ Of all CONSORT-PRO items considered together in our study, the rating of a correct report was lower than it was in those 3 reviews. For example, contrary to our study, Bylicki et al³⁸ found 10 trials that correctly reported all 5 main specific extensions of the CONSORT-PRO statement. This emphasizes the poor PRO consideration in patients with glioblastoma. In our study, the OQS was not associated with the date of publication. Quality of reporting was improved when PROs were reported in secondary dedicated publications, when targeted dimensions were described, and when results were reported using texts, graphics, and tables together. We might hypothesize that this could be due to the relatively greater concern regarding PROs by trained authors, and the undoubtedly greater space allocated in a dedicated manuscript. When analyses of PROs were not exploratory, there was a large variation in the quality of reporting. Basically, the description of the PRO hypothesis and the identification of its relevant domains were reported in 10% and 3% trials, respectively, contrary to other reviews where these items were reported more frequently (between 10% and 73%).³⁸⁻⁴⁰

One of the most important items included in the 2013 CONSORT extension is the explanation of statistical approaches for addressing missing data.³² Missing data can bias the way of analyzing longitudinal HRQoL data if it is not adequately explained.⁴² Patients may drop out because of deterioration of health status, cognitive functions, or

death; and the level of missing PRO data is often high.³² This could induce a risk of selecting a population with better HRQoL levels and not adjusting for missing data, thus limiting the robustness of the results. Moreover, the number of participants reporting HRQoL data at baseline and at subsequent time points should be made transparent, especially when missing data are due to deterioration of health status. In our review, these 2 items were reported in 55% and 43% of the RCTs, respectively. Furthermore, 6 trials (14%) described the statistical approaches for dealing with missing data. Hence, the reporting of PRO data and the statistical approaches of analysis of missing data need to be standardized. Analyses performed for longitudinal PROs data are multiple. The 2 main robust methods recommended to date are the LMM and TTD.^{43–45} In our review, the most broadly used method is the descriptive mean change from baseline (41%). The LMM method was used in 12 studies (35%) and the TTD method in 10 trials (29%). Preceding analysis for longitudinal HRQoL data, the MCID should be *a priori* determined.³³ In our review, it was clearly specified in 50% of the studies. The MCID represents the smallest change in HRQoL score identified as clinically important. For example, a difference ranging from 5 points to 10 points could be considered as the MCID for the EORTC questionnaires.⁴⁶ In patients with glioblastoma, the smallest changes in HRQoL conventional scores have not been clearly determined. In our review, the 16 studies that used 1 of the 3 EORTC questionnaires and stated the MCID used a 10-point decrease in the global HRQoL score as the MCID.

Recommendations on the schedule of PRO assessment should be correctly provided.⁴⁷ In our study, only 27% of trials provided at least 3 HRQoL assessments (at baseline, during treatment, and at the end of the study), as recommended by EORTC.^{47,48} Additionally, authors should pay attention to the timing of diagnostic procedures, which could influence HRQoL results, specifically with glioblastoma, a life- and cognitive function-threatening cancer.

The majority of articles that we have reviewed, mostly those after 2013, were published in journals that emphasized the CONSORT statement. We cannot exclude that limited journal space could explain the lack of precision in a subset of the articles and authors may not often report all the methodology and the results of PRO. Bylicki and colleagues explored the space allocated to PRO data when reported in the main manuscript: It was 16% and 10% in the “Methods” and “Results” sections, respectively.³⁸ We have also confirmed that a secondary publication dedicated to PRO results and a more detailed reporting of the results (ie, texts, graphics, and tables) are both associated with a higher OQS.

In patients with glioblastoma, the association between HRQoL and survival is conflicting mostly because not all studies demonstrate additional prognostic value.^{49–52} However, HRQoL assessments in neuro-oncological clinical trials are now essential to provide important information for the assessment of perceived clinical benefits and risks of a new treatment.⁵³ Indeed, tumor location is responsible for rapid symptom impairment of HRQoL, and disease progression is often associated with clinical deterioration. Patients and physicians confront disabling

symptoms, HRQoL impairment, reduced autonomy, frailty, and disability. Additionally, patient follow-up informs clinicians about the effect of treatment. However, the majority of trials did not report PROs at all (see Figure 1), which is consistent with what has already been published.³⁸ The publication of RCTs primarily concern clinical issues in oncology. However, authors should be careful about “evidence-based medicine” because it is more often based on trials than on objective observations of the patient’s life. This review is an inventory of current trends regarding the state of PROs and quality of life assessments in glioblastoma trials. At present, there is no compelling consensus as to the best methods of PRO reporting in RCT, hampering interpretation of results. The CONSORT-PRO statements are recommendations that authors should endorse to improve reporting of PROs in publications. They are not mandatory but allow readers to judge the strength of the design, analysis, and interpretation of PROs end points (primary, secondary, or ancillary).

We observed throughout our review praise for survival with few considerations relating to the quality of life defined by the patient himself or herself. For constructing future RCTs involving patients with glioblastoma, we believe trials should use coprimary end points (eg, survival and quality of life) whenever possible. Also, when a PRO is a secondary or ancillary end point, an entire dedicated second manuscript should be proposed. A harmonized, tripartite team of statisticians/methodologists specializing in quality of life in oncology, neurologists, and oncologists should gather to develop and expand trials. Regarding statistical approach, the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) consortium was formed to enhance the methodological practice of PRO measurement. This group recently published a set of recommendations focusing on appropriate statistical methods to use for PRO analysis and on standardizing how to address missing data.⁵⁴ We further advocate the use of a questionnaire that mixes global and neurological symptoms as well as well-being, along with prespecified targeted dimensions. Then, when a trial focuses on quality of life, the manuscript should be reviewed to check specifically for use of the CONSORT-PRO statements.

In conclusion, our data highlight the poor quality and the heterogeneity of the measurement, analysis, and reporting of PROs in glioblastoma trials. The exceptions were when PROs were reported in a dedicated manuscript, when targeted dimensions were prespecified, and when trials reported results with texts, graphic, and tables, emphasizing the lack of space in manuscripts in which PROs are not the main topic. Use of the CONSORT-PRO statement should be advocated to better embrace today’s expectations of a cancer trial, specifically regarding patients with glioblastoma. Another challenge would be to provide new PRO questionnaires adapted to toxicities arising from new treatments (eg, targeted therapies and immunotherapy).³⁴

Ethical approval was not required because of the review nature of the research. Because this is a retrospective review of data from previously published studies, patient informed consent procedures were not required.

Supplementary material

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