

Reporting standards in randomized controlled trials involving neuro-oncology caregivers: A systematic review report from the RANO-Cares working group

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Abstract

Background. Family caregivers in neuro-oncology (eg, spouse, family member, friend to a patient) have high unmet support needs, yet intervention trials and effective support options are scarce. The Response Assessment in Neuro-Oncology (RANO)-Cares working group investigated the methodological quality of neuro-oncology caregiver outcomes reporting in randomized controlled trials (RCTs).

Methods. A systematic review was performed to evaluate to what extent RCTs assessing outcomes of caregivers of adult primary brain tumor patients adhere to minimum reporting standards. A 33-item checklist (23 applicable to secondary analysis reports) based on the International Society for Quality of Life Research (ISOQOL) criteria for patient-reported outcome reporting was used. Risk of bias was assessed per RCT.

Results. Fifteen publications from 11 unique RCTs included 676 neuro-oncology caregivers, with low overall risk of bias. Ten publications (66%) reported on caregiver outcomes as a primary aim, of which 8 (80%) satisfied $\geq 2/3$ of the key methodological criteria. Of the 5 secondary analysis reports (33%), 2 (40%) met $\geq 2/3$ of applicable key criteria. Criteria often not reported adequately included sample size calculations (reported adequately in $n = 8$, 53%), participant flow ($n = 9$, 60%) window for data collection ($n = 1$, 6%), and extent of ($n = 10$, 66%), reasons for ($n = 9$, 60%), and statistical approaches in dealing with ($n = 4$, 26%) missing data.

Conclusions. Whilst there are opportunities to enhance reporting standards, RCTs that include neuro-oncology caregiver outcomes generally adhere to high-quality reporting standards and have low risk of bias, indicating good potential to impact clinical practice.

Keywords

brain tumor | caregiver | PRO | reporting standards | systematic review

Partners, family members, or friends who act as family caregivers to provide practical, physical, or emotional support for patients diagnosed with a brain tumor consistently report high levels of unmet information and support needs.^{1–4} This can lead to significant burden, consequently impacting caregiver and patient health and well-being.^{5–7} Furthermore, a consistent negative impact of neuro-oncology-specific disease burden on family functioning has been identified throughout the trajectory of brain cancer.⁸

Caregiver-specific support resources are typically scarce. In a survey of 42 Australian healthcare professionals, 35 provided information on care for family caregivers. Most were able to refer caregivers to services (social worker/welfare officer; care coordinator/nurse navigator; psychologist) and about half could offer a referral to a support group as well.⁹ Yet, in a survey of 103 healthcare professionals from 23 countries, 37% of respondents rated services for caregivers as inadequate.¹⁰ While some support may be accessible outside of

the hospital setting, for example through primary care or brain tumor charities, timely access for caregivers can be challenging. Internationally, there is growing recognition of the importance of caregivers in the optimal treatment, management, and support of patients with brain tumors. This creates unique opportunities to support caregivers—yet, the low certainty of evidence regarding effectiveness of neuro-oncology caregiver interventions^{11,12} complicates widespread implementation.

Undertaking rigorous randomized controlled trials (RCTs) of neuro-oncology caregiver support interventions is costly and time-consuming. The typically complex and often multimodal intervention programs (eg, psychosocial support, psychoeducation, delivered individually or to both patient and caregiver together) can include different (combinations of) components and are evaluated by using a wide variety of outcome measures. There is not only a lack of consensus on the key constructs that should be assessed but also the chosen outcome measures vary widely as a systematic review of 157 publications from 120 neuro-oncology caregiver studies showed.¹³ Without more consideration for the standardization of data collected on specific constructs and outcome measures it is difficult to compare study outcomes and ultimately, to gauge impact and decide which interventions yield the best results. Potential undesired consequences of this lack of agreement can be a lack of implementation of effective interventions or conversely, investment of resources in the implementation of interventions that are not effective, which then take up valuable time and headspace of caregivers in dire need of support.

The importance of high-quality neuro-oncology patient-reported outcomes (PROs) has gained recognition over the past 5–10 years.^{14–16} Even when there is consensus on the core constructs and outcome measures to be used in neuro-oncology caregiver research, informed decisions on the impact of an intervention can only be made if the level of evidence of caregiver-reported outcomes and its reporting is of sufficient high quality. The Response Assessment in Neuro-Oncology (RANO)-Cares working group has been created to evaluate and help guide caregiver-related research outcomes in neuro-oncology. This group will assess key constructs and measurement tools that should be included in clinical trials, and how caregiver outcomes should be reported. As a first step, we investigated the current state of methodological quality of reporting on caregiver outcomes in neuro-oncology RCTs.

Methods

Study Design

This systematic literature review aimed at evaluating to what extent randomized controlled trials (RCTs), which include neuro-oncology caregiver outcomes (any type, including, eg, questionnaire-based outcomes and qualitative outcomes, included as either a primary or secondary/tertiary outcome), adhere to minimum reporting standards. Where applicable, we followed PRISMA reporting guidelines.¹⁷ Due to the nature of the review study (no human participants), ethical approvals were not required.

Search Strategy

We updated searches conducted for our previous systematic review,¹³ which aimed to identify all published literature covering adult caregivers of adult patients with brain tumors (search date: July 6, 2023). The searches conducted in PubMed/Medline, Embase, Web of Science, Emcare, Cochrane Library, and PsycINFO consisted of a combination of terms for (1) informal caregivers of adult patients diagnosed with primary brain tumors, (2) outcomes/constructs, (3) outcome measures, and (4) RCTs. Development of search terms was guided by terminology used in previous research, existing frameworks, and expert opinion. [Supplementary File 1](#) includes search strings for PubMed, which were adapted for the other databases.

Study Selection

All citations identified in the searches were imported into Covidence,¹⁸ after removal of duplicates. Articles were included according to the criteria displayed in [Table 1](#). Importantly, any article reporting on caregiver data from RCTs was eligible—hence, these could be main outcomes reports or secondary analyses, reporting on caregiver outcomes as a primary or secondary/tertiary aim, as reporting standards should be high regardless of the number of publications resulting from one RCT. Titles and abstracts were screened against inclusion criteria by 2 reviewers (FW.B., P.S., and/or L.D.) independently. Full texts of potentially relevant articles were added into Covidence and assessed by 2 reviewers (FW.B., P.S., L.D., K.P., and/or C.H.) independently. At both stages, differing opinions were discussed until agreement was reached, guided by a third researcher if needed. All decisions were coded and recorded in Covidence. Reviewers were not blinded to journal titles, authors, or institutions.

Data Extraction

An excel-based data extraction form was drafted and piloted prior to starting data extraction. Data extracted included basic study information (title, author, year, country where data were collected, funding), study population details (caregiver participants, patient populations, sociodemographic information), and study characteristics (eg, type of intervention, primary endpoint, main results, instruments used). Missing data were recorded as “not known”; study authors were not contacted. To assess the level of reporting of caregiver-reported outcomes, we adapted the checklist developed by the International Society for Quality of Life Research (ISOQOL).¹⁹ The checklist contains 17 items, which should apply to all RCTs, with an additional 11 items applicable when a PRO is the primary endpoint. To enhance comparability to a previously published similar effort undertaken in RCTs reporting on PROs in neuro-oncology patients,¹⁶ we similarly split the missing data item from the ISOQOL checklist into 2 items (extent of missing data and statistical approaches to deal with missing data). Where needed, items were rephrased for the caregiver context (eg, replacing “patient-reported”

Table 1. In- and Exclusion Criteria for Study Selection

Inclusion Criteria	Exclusion Criteria
<i>Types of participants</i>	
Studies covering adult caregivers (current or bereaved) of adult patients with primary brain tumors.	Studies involving caregivers under <18 years of age
In samples that included caregivers of both young and adult patients, studies were included if adult (18+) patients made up at least 90% of the sample.	Studies involving only caregivers of childhood brain tumor patients or childhood brain tumor patients who are now adults
Studies reporting on mixed caregiver populations (eg, acquired brain injury or cancer) were included, as long as primary brain tumors were part of the sample.	Studies involving only caregivers of patients with metastatic brain tumors.
<i>Types of studies</i>	
Randomized controlled trials, reporting on caregiver outcomes and/or outcome measures.	Any other original research designs (eg, nonrandomized or noncontrolled intervention studies; observational studies)
	Reviews (not original research)
	Non-peer-reviewed studies
	Conference abstracts
	Gray literature
	Studies in which caregivers are included as the proxy reporter for patients
<i>Geographical coverage</i>	
Any setting, any country	N/A
<i>Language</i>	
Published in English, Dutch, Danish, French, or German.	Published in languages other than English, Dutch, Danish, French, or German

by “caregiver-reported”). Four further items (electronic mode of administration; outcomes reported in graphical format; outcome interpretation; clinical significance methods) were added to enhance comparability to a similar review performed in neuro-oncology patient RCTs.¹⁶ All authors contributed to data extraction, with details on each study extracted by 2 individual reviewers (L.D.; C.H.; P.S.; D.C.; J.S.Y.; T.W.; M.S.; E.R.A.; K.P.). Reviewers did not extract data from publications they co-authored. A third author (F.W.B.) then performed a consensus check for each publication before data extraction was finalized.

Synthesis

Data were processed in SPSS version 28. Characteristics of included studies and adherence to reporting criteria were analyzed with descriptive statistics. The revised Cochrane risk of bias tool was used to estimate risk (low/unclear/high) of selection bias, performance bias, detection bias, attrition bias, and reporting bias.²⁰ The risk of bias figure was generated using robvis.²¹ To estimate the potential impact of study evidence on clinical practice decisions, we determined, in line with previous research^{16,22} that only those studies meeting at least two-thirds of the criteria should be rated as high quality. This equates to >22/33 criteria for publications that include caregiver outcomes as a main aim and >15/23 criteria for publications that report on caregiver outcomes as secondary analyses. The evidence from studies scoring above the cutoff was synthesized narratively.

Results

Characteristics of Included Publications

The 15 publications covered 11 unique RCTs (see [Figure 1](#), [Table 2](#)). Ten publications (67%) reported on caregiver outcomes as primary study aim; 5 (33%) as a secondary aim. Interventions were described as meaning-centered psychotherapy for caregivers,^{23,24} a nurse-led online needs-based caregiver intervention (SmartCare),^{26,27} a structured program of cognitive behavioral therapy and psychoeducation for caregivers,²⁵ internet-based guided self-help for glioma patients with depressive symptoms,²⁸ a structured multidisciplinary psychosocial intervention for patients,²⁹ a supportive educational intervention for caregivers (Care-IS),³⁰ cognitive rehabilitation and problem-solving therapy for patients,³¹ a dyadic or individual caregiver yoga intervention,^{32,33} an online couple-based meditation intervention,^{34,35} and an electronic support network assessment program (eSNAP) for caregivers.^{36,37} Five RCTs were described as definitive trials^{25,26,28–30} and 6 as pilot trials.^{23,31–34,36}

Reports were published in peer-reviewed journals between 2008 and 2023, with half ($N = 7$) published after 2020. Eleven reports (79%) originated from the United States, 2 (14%) from the Netherlands, and 1 (7%) from Australia. Across publications, 778 unique caregiver study participants (676 neuro-oncology caregivers) were reported (range 8–188). All reports focused on adult populations

Table 2. Study Characteristics

RCT Number	Intervention	First Author (Year)	Type of Trial as Described in Publication	Country	Disease Group	Population Reported on	Caregiver Sample Size	Outcome Measures	Main Aim	Intervention	Reported $\geq 2/3$ of ISOQOL Criteria?
1	Meaning-centered psychotherapy for caregivers	Applebaum (2022) ²³	Pilot	United States	Primary malignant brain tumors	Caregivers	55	Psychosocial services use. Intervention preferences. Perceived barriers. Distress Thermometer. Life Attitude Profile-Revised. Attitudes Towards Caregiving Scale. Caregiver Reaction Assessment. Hospital Anxiety and Depression Scale. Functional Assessment of Chronic Illness Therapy—Spiritual Well-Being 12-Item Scale Duke-UNC Functional Social Support Questionnaire. Benefit Finding Scale.	To evaluate the feasibility, acceptability, and preliminary efficacy of MCP-C among caregivers	Meaning-centered psychotherapy for caregivers	Yes
		Applebaum (2022) ²⁴	Pilot	United States	Primary malignant brain tumors	Caregivers	9	Semi-structured and individual interviews with caregivers.	To refine and improve a Meaning-Centered Psychotherapy for Cancer Caregivers (MCP-C) intervention manual so that it can most effectively assist caregivers in experiencing meaning and purpose	Meaning-centered psychotherapy for caregivers	No
2	Structured program of cognitive behavioral psychoeducation for caregivers	Boele (2013) ²⁵	Definitive	The Netherlands	Primary malignant brain tumors	Caregivers	56	MOS 36-item short-form health survey (SF-36). Caregiver Mastery Scale.	To determine whether HRQOL and neurological symptoms of the patient as perceived by caregivers are related to the informal caregiver's HRQOL and feelings of mastery. To determine, whether a cognitive behavioral therapy (CBT) intervention enhances HRQOL and feelings of mastery of informal caregivers of HGG patients	Structured program of cognitive behavioral therapy and psychoeducation	Yes

Table 2. Continued

RCT Number	Intervention	First Author (Year)	Type of Trial as Described in Publication	Country	Disease Group	Population Reported	Caregiver Sample Size	Outcome Measures	Main Aim	Intervention	Reported $\geq 2/3$ of ISOQOL Criteria?
3	Nurse-led online needs-based caregiver intervention (SmartCare) for caregivers	Boele (2022) ²⁶	Definitive	United States	Primary malignant brain tumors	Caregivers	120	Caregiver needs screen. Center for Epidemiological Studies-Depression scale. Profile of Mood States Anxiety. Caregiver Reaction Assessment. Caregiver Mastery.	To determine the impact of a caregiver intervention on caregivers' emotional health	Nurse-led online needs-based caregiver intervention (SmartCare)	Yes
4	Internet-based guided self-help Structured multidisciplinary psychosocial intervention for patients	Boele (2019) ²⁷	Definitive	United States	Primary malignant brain tumors	Caregivers	122	Caregiver needs screen. Center for Epidemiological Studies-Depression scale. Profile of Mood States Anxiety. Caregiver Reaction Assessment; Caregiver Mastery.	To determine the psychometric properties of a neuro-oncology caregiver needs screen	Nurse-led online needs-based caregiver intervention (SmartCare)	Yes
4	Internet-based guided self-help Structured multidisciplinary psychosocial intervention for patients	Boele (2020) ²⁸	Definitive	The Netherlands	Primary brain tumors	Caregivers and patients	45	Trimbos/iMTA questionnaire for costs associated with Psychiatric Illness. Short-Form Health and Labor Questionnaire. Epidemiological Studies-Depression Scale. Checklist Individual Strength. MOS cognitive functioning scale. EORTC brain cancer module.	To explore healthcare and societal costs in glioma patients at high risk for depression and their family caregivers, and explore relationships between costs and treatable symptoms	Internet-based guided self-help	Yes
5	Structured multidisciplinary psychosocial intervention for patients	Clark (2013) ²⁹	Definitive	United States	Mixed neuro-oncologic groups	Caregivers and patients	131 (29 neuro-oncology)	ECOG performance status. MMSE. Beck Depression Inventory-II. FACT-G. Caregiver Quality of Life Index-Cancer Scale.	To replicate a prior study to determine whether a multidisciplinary intervention can maintain the QOL of patients with advanced cancer who are actively receiving radiotherapy	Structured multidisciplinary psychosocial intervention for patients	No

Table 2. Continued

RCT Number	Intervention	First Author (Year)	Type of Trial as Described in Publication	Country	Disease Group	Population Reported on	Caregiver Sample Size	Outcome Measures	Main Aim	Intervention	Reported $\geq 2/3$ of ISOQOL Criteria?
6	Supportive educational intervention for caregivers	Halkett (2023) ³⁰	Definitive	Australia	Primary malignant brain tumors	Caregivers	188	Palliative Care Needs Assessment Tool. Integrated Palliative Outcome Scale. Preparedness for Caregiving Scale. Distress Thermometer. Hospital Anxiety and Depression Scale. Caregiver Quality of Life Index-Cancer. Carer Competence Scale. Modified Caregiver Strain Index.	To determine the effect of a nurse-led intervention on caregiver preparedness and distress	Supportive educational intervention for caregivers (Care-IS)	Yes
7	Combined cognitive rehabilitation and problem-solving intervention for patients and caregivers	Locke (2008) ³¹	Pilot	United States	Primary brain tumors	Caregivers and patients	19	A study-specific Post-Study Feedback Questionnaire. MPAL-4 = Mayo-Portland Adaptability Inventory-4. Linear Analogue Self-Assessment (LASA) scale. The Caregiver QOL Index-Cancer (COOLC). The Profile of Mood States (POMS).	To determine the feasibility and tolerability of a combined cognitive-rehabilitation and problem-solving therapy intervention for patients with brain tumors and their caregivers	Cognitive rehabilitation and problem-solving therapy	No
8	Dyadic yoga program for patients and caregivers	Milbury (2019) ³²	Pilot	United States	Primary brain tumors	Caregivers and patients	20	Depressive symptoms (Center for Epidemiological Studies-Depression measure): CES-D. Brief Fatigue Inventory (BFI) QoL. The Medical Outcomes Study 36-item short-form survey (SF-36). Borg Rating of Perceived Exertion Scale (satisfaction).	To examine the feasibility and preliminary efficacy of a dyadic yoga (DY) intervention as a supportive care strategy	Dyadic yoga intervention	Yes

Table 2. Continued

RCT Number	Intervention	First Author (Year)	Type of Trial as Described in Publication	Country	Disease Group	Population Reported on	Caregiver Sample Size	Outcome Measures	Main Aim	Intervention	Reported $\geq 2/3$ of ISOQOL Criteria?
9	Dyadic or individual yoga program for caregivers	Milbury (2023) ³³	Pilot	United States	Primary malignant brain tumors	Caregivers and patients	67	Rates of consent (including refusal reasons). Session attendance. Assessment completion. Program evaluation. Centers for Epidemiological Studies-Depression (CES-D); Medical Outcomes Study 36-item. Short-form survey (SF-36). Caregiver Reaction Assessment (CRA). Semi-structured individual interviews.	To compare the feasibility and preliminary efficacy of a dyadic yoga (DY) versus an individual caregiver yoga (CY) intervention	Dyadic or individual caregiver yoga intervention	Yes
10	Online couple-based meditation for patients and caregivers	Milbury (2020) ³⁴	Pilot	United States	Primary and metastatic brain tumors	Caregivers and patients	35	Feasibility. Patient symptom severity (MDASI-BT). Patient and caregiver depressive symptoms (CES-D). Patient and caregiver mindfulness (Mindful Attention Awareness Scale). Patient and caregiver compassion and caregiver compassion (Self-compassion Scale. Patient and caregiver intimacy (Personal Assessment of Intimacy in Relationships Inventory).	To examine the feasibility of implementing a randomized controlled trial of a couple-based meditation intervention delivered via videoconference	Four sessions of mindful meditation for both dyad members	Yes
11	Electronic social support and resource visualization tool for caregivers	Whisenant (2022) ³⁵ Reblin (2018) ³⁶ Reblin (2018) ³⁷	Pilot Pilot Pilot	United States United States United States	Brain tumors not specified Primary brain tumors Primary brain tumors	Caregivers Caregivers Caregivers	8 40 40	Semi-structured interviews Zarit Caregiving Burden Scale. Hospital Anxiety and Depression Scale. Satisfaction with social support scale (study-specific). A study-specific "likeability/usability" questionnaire (eg, willingness to participate, intervention acceptance, follow-up rates).	To describe the experience of caregivers who have lost a partner with a CNS tumor To describe preliminary efficacy and outcomes of the eSNAP intervention To assess the feasibility of eSNAP to automate the capture and visualization of family caregiver social network data	Couple-based mind-body intervention Electronic support network assessment program (eSNAP) Electronic support network assessment programme (eSNAP)	No Yes No

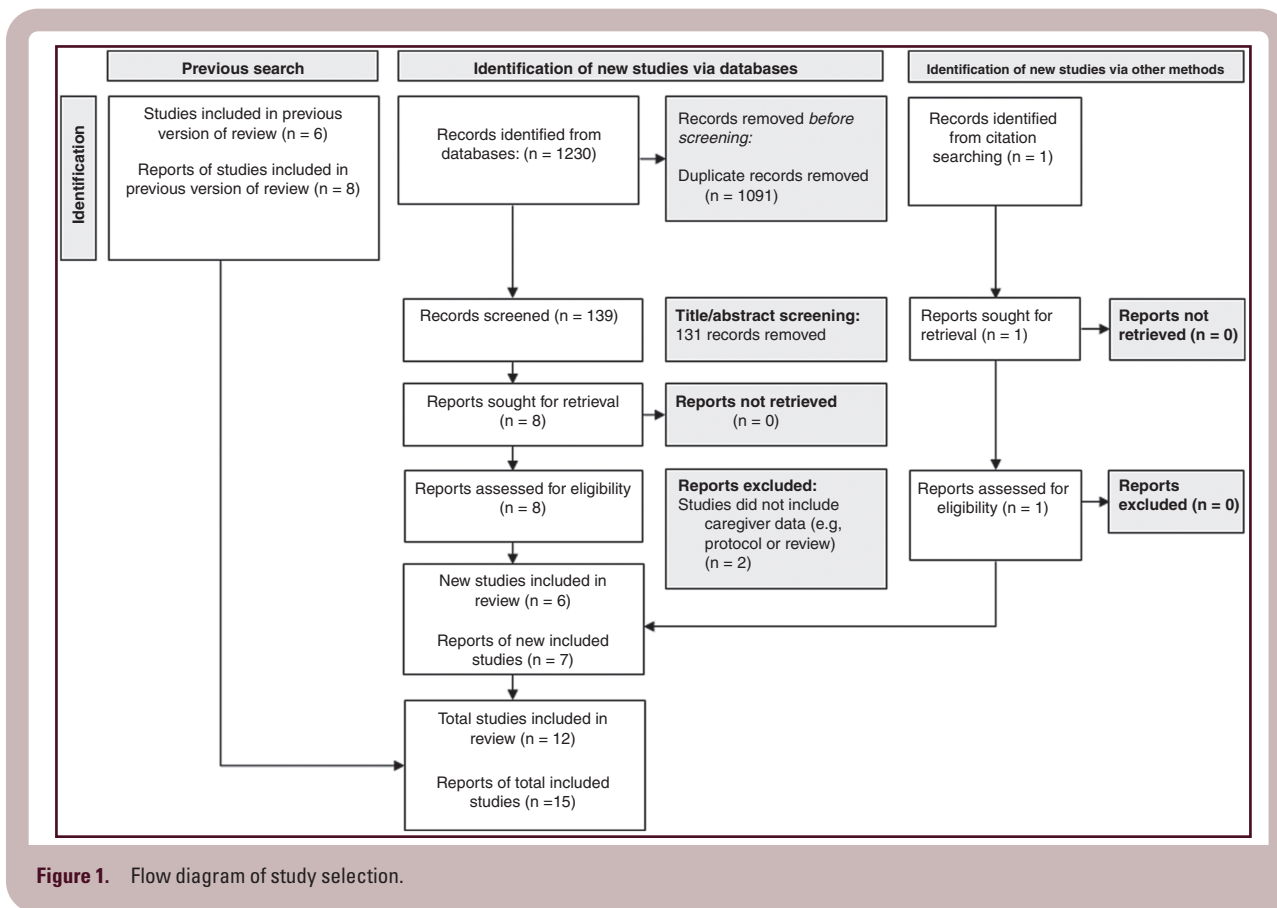


Figure 1. Flow diagram of study selection.

with the exception of Milbury et al. (2023),³³ who included both adult and pediatric patient groups. Between 0 and 9 validated outcome measures were reported in the 11 unique studies, with 4 studies (also) using study-specific questionnaires and/or qualitative interviews. None of the studies appeared to be industry-sponsored (in part or full).

Methodological Reporting Quality

Of the 11 unique RCTs, 9 (82%; 8 primary and 1 secondary analysis report)^{23,25,26,30,32–34,37,38} reports satisfied $\geq 2/3$ of the key methodological criteria, signaling high enough reporting quality to impact clinical practice. Of the 2 RCTs not meeting $\geq 2/3$ of the key methodological criteria,^{29,31} 1 was a secondary analysis report.²⁹

Table 3 depicts the results related to the methodological criteria per RCT (with caregiver outcomes as the primary or nonprimary endpoint) and per publication (with caregiver outcomes as the primary or nonprimary endpoint). Several criteria were not reported adequately (defined as $>50\%$ of cases per cell of Table 3), with details provided below. Not all criteria were applicable to all reports (eg, those reporting on qualitative findings), this was taken into account.

The windows for valid caregiver-related outcome responses (ie, the timeframe within which outcomes would need to be collected to fall under a specific timepoint in RCT analyses) were not specified in 11 RCTs (100%), or 14 publications (93%). In 5 RCTs (45%), or 7 publications (47%), sample size calculations were not reported in

sufficient detail. Related to statistical methods, the extent of missing data was not adequately reported in 4 RCTs (36%), or 5 publications (33%). The statistical approaches for dealing with missing data were not explicitly stated in 9 RCTs (82%), or 10 publications (67%). The methods used to deal with multiple comparisons were not reported adequately in 9 RCTs (82%), or 11 publications (73%). Reasons for missing data were not covered in 4 RCTs (36%), or 6 publications (40%). Graphical depictions of caregiver-related outcomes were not used frequently (not used in 7 RCTs [64%], or 11 publications [73%]). In those studies where it would be relevant, 86%–88% (6 out of 7 RCTs; 7 out of 8 publications) did not take survival differences between treatment groups into account for analysis. In the discussion of findings, the limitations of caregiver outcome components of the trial were not adequately covered in 2 RCTs (18%), or 4 publications (27%). Where applicable, 7 out of 9 RCTs (78%), or 8 out of 13 (62%) publications did not cover the methodology used to assess clinical significance in the interpretation of findings. Finally, where a new instrument (nonvalidated tool) was used, 6 out of 8 RCTs (75%) or 10 out of 12 publications (83%) did not provide a copy as supplemental material.

Risk of Bias

The risk of bias assessments for the 11 RCTs included in this review did not reveal major concerns, see Figures 2 and 3.

Table 3. Reporting Standards in Neuro-Oncology Caregiver Publications as Per Adapted International Society for Quality of Life Research (ISOQOL) Recommended Standards

Is the caregiver-reported outcome the primary endpoint?		RCTs (N = 11)		Publications (N = 15)	
		Primary (N = 8)	Nonprimary (N = 3)	Primary (N = 10)	Nonprimary (N = 5)
<i>Title and abstract</i>					
The caregiver-related outcomes should be identified as an outcome in the abstract	Yes	7 (87.5%)	3 (100%)	9 (90%)	5 (100%)
	No	1 (12.5%)	0 (0%)	1 (10%)	0 (0%)
The title of the paper should be explicit as to the RCT including a caregiver-related outcome	Yes	7 (87.5%)	2 (67%)	9 (90%)	4 (80%)
	No	1 (12.5%)	1 (33%)	1 (10%)	1 (20%)
<i>Introduction, background, and objectives</i>					
The hypothesis regarding caregiver-related outcomes should be stated and should specify the relevant domain(s), if applicable	Yes	7 (87.5%)	2 (67%)	9 (90%)	3 (60%)
	No	1 (12.5%)	0 (0%)	1 (10%)	0 (0%)
	Not applicable	0	1 (33%) ^a	0 (0%)	2 (40%) ^{a,b}
The introduction should contain a summary of caregiver-related outcome research that is relevant to the RCT	Yes	7 (87.5%)	2 (67%)	9 (90%)	4 (80%)
	No	1 (12.5%)	1 (33%)	1 (10%)	1 (20%)
Additional details regarding the hypothesis should be provided, including the rationale for the selected domain(s), the expected direction(s) of change, and the time points for assessment	Yes	5 (62.5%)	1 (33%)	6 (60%)	1 (20%)
	No	3 (37.5%)	1 (33%)	4 (40%)	2 (40%)
	Not applicable	0 (0%)	1 (33%) ^a	0 (0%)	2 (40%) ^{a,b}
<i>Methods/outcomes</i>					
The mode of administration of the instruments and the methods of collecting data should be described	Yes	5 (62.5%)	3 (100%)	7 (70%)	4 (80%)
	No	3 (37.5%)	0 (0%)	3 (30%)	1 (20%)
A citation for the original development of the caregiver-related outcome instrument(s) should be provided	Yes	8 (100%)	3 (100%)	10 (100%)	3 (60%)
	No	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Not applicable	0 (0%)	0 (0%)	0 (0%)	2 (40%) ^c
Electronic mode of administration*	Yes	3 (37.5%)	2 (67%)	5 (50%)	2 (40%)
	No	4 (50%)	0 (0%)	4 (40%)	1 (20%)
	Not reported	1 (12.5%)	1 (33%)	1 (10%)	2 (40%)
The rationale for choice of the instrument(s) used should be provided	Yes	8 (100%)	3 (100%)	9 (90%)	4 (80%)
	No	0 (0%)	0 (0%)	1 (10%)	1 (20%)
Evidence of instrument validity and reliability should be provided or cited (rated "no" if all instruments were not validated)	Yes	8 (100%)	3 (100%)	9 (90%)	3 (60%)
	No	0 (0%)	0 (0%)	1 (10%)	2 (40%)
The intended caregiver-related outcome data collection schedule should be provided	Yes	8 (100%)	3 (100%)	10 (100%)	5 (100%)
	No	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Caregiver-related outcomes should be identified in the trial protocol; post hoc analyses should be identified	Yes	8 (100%)	3 (100%)	10 (100%)	3 (60%)
	No	0 (0%)	0 (0%)	0 (0%)	1 (20%)
	Not applicable	0 (0%)	0 (0%)	0 (0%)	1 (20%) ^c
The status of caregiver-related outcomes as either a primary or secondary outcome should be stated	Yes	7 (87.5%)	3 (100%)	9 (90%)	4 (80%)
	No	1 (12.5%)	0 (0%)	1 (10%)	1 (20%)
Windows for valid caregiver-related outcome responses should be specified and justified as being appropriate for the clinical context	Yes	0 (0%)	0 (0%)	0 (0%)	1 (20%)
	No	8 (100%)	3 (100%)	10 (100%)	4 (80%)
<i>Sample size</i>					
There should be a power/sample size calculation relevant to the caregiver-related outcome based on a clinical rationale (eg, anticipated effect size)	Yes	4 (50%)	2 (67%)	5 (50%)	3 (60%)
	No	4 (50%)	1 (33%)	5 (50%)	2 (40%)
<i>Statistical methods</i>					
There should be evidence of appropriate statistical analysis and tests of statistical significance for each hypothesis tested (if applicable)	Yes	7 (87.5%)	3 (100%)	8 (80%)	3 (60%)
	No	1 (12.5%)	0 (0%)	2 (20%)	0 (0%)
	Not applicable	0 (0%)	0 (0%)	0 (0%)	2 (40%) ^c

Table 3. Continued

Is the caregiver-reported outcome the primary endpoint?		RCTs (N = 11)		Publications (N = 15)	
		Primary (N = 8)	Nonprimary (N = 3)	Primary (N = 10)	Nonprimary (N = 5)
The extent of missing data should be stated	Yes	5 (62.5%)	2 (67%)	7 (70%)	3 (60%)
	No	3 (37.5%)	1 (33%)	3 (30%)	2 (40%)
Statistical approaches for dealing with missing data should be explicitly stated	Yes	2 (25%)	0 (0%)	3 (30%)	1 (20%)
	No	6 (75%)	3 (100%)	7 (70%)	3 (60%)
	Not applicable	0 (0%)	0 (0%)	0 (0%)	1 (20%) ^c
The manner in which multiple comparisons have been addressed should be provided	Yes	1 (12.5%)	1 (33%)	1 (10%)	1 (20%)
	No	7 (87.5%)	2 (67%)	9 (90%)	2 (40%)
	Not applicable	0 (0%)	0 (0%)	0 (0%)	2 (40%) ^c
Results/participant flow					
A flow diagram or a description of the allocation of participants and those lost to follow-up should be provided for caregiver-related outcomes specifically	Yes	6 (75%)	1 (33%)	8 (80%)	1 (20%)
	No	2 (25%)	1 (33%)	2 (20%)	1 (20%)
	Not applicable	0 (0%)	1 (33%) ^d	0 (0%)	3 (60%) ^d
The reasons for missing data should be explained	Yes	7 (87.5%)	0 (0%)	8 (80%)	1 (20%)
	No	1 (12.5%)	3 (100%)	2 (20%)	4 (80%)
Baseline data					
The study patients characteristics should be described including baseline caregiver-related outcome scores	Yes	6 (75%)	2 (67%)	8 (80%)	4 (80%)
	No	2 (25%)	1 (33%)	2 (20%)	1 (20%)
Outcomes and estimation					
Are caregiver-related outcomes also reported in a graphical format? [*]	Yes	3 (37.5%)	1 (33%)	3 (30%)	1 (20%)
	No	5 (62.5%)	2 (67%)	7 (70%)	4 (80%)
The analysis of caregiver-related outcome data should account for survival differences between treatment groups, if relevant	Yes	1 (12.5%)	0 (0%)	1 (10%)	0 (0%)
	No	4 (50%)	2 (67%)	5 (50%)	2 (40%)
	Not applicable	3 (27.5%) ^{d,e}	1 (33%) ^d	4 (40%) ^{d,e}	3 (60%) ^{d,e}
Results should be reported for all caregiver-related outcome domains (if multidimensional) and items identified by the reference instrument (ie, not just those that are statistically significant)	Yes	8 (100%)	3 (100%)	10 (100%)	3 (60%)
	No	0 (0%)	0 (0%)	0 (0%)	2 (40%)
The proportion of participants achieving predefined responder definitions should be provided where relevant	Yes	5 (62.5%)	1 (33%)	7 (70%)	1 (20%)
	No	2 (25%)	0 (0%)	2 (20%)	0 (0%)
	Not applicable	1 (12.5%) ^f	2 (67%) ^{a,f}	1 (10%) ^f	4 (80%) ^{a,b,c,f}
Discussion/limitations					
The limitations of the caregiver-related outcome components of the trial should be explicitly discussed	Yes	7 (87.5%)	2 (67%)	9 (90%)	2 (40%)
	No	1 (12.5%)	1 (33%)	1 (10%)	3 (60%)
Generalizability					
Generalizability issues uniquely related to the caregiver-related outcome results should be discussed	Yes	7 (87.5%)	2 (67%)	9 (90%)	4 (80%)
	No	1 (12.5%)	1 (33%)	1 (10%)	1 (20%)
Interpretation					
Are caregiver-related outcomes interpreted? (Not only restated) [*]	Yes	7 (87.5%)	3 (100%)	9 (90%)	5 (100%)
	No	1 (12.5%)	0 (0%)	1 (10%)	0 (0%)
The clinical significance of the caregiver-related outcome findings should be discussed	Yes	6 (75%)	3 (100%)	8 (80%)	5 (100%)
	No	2 (25%)	0 (0%)	2 (20%)	0 (0%)
Methodology used to assess clinical significance (in case this was addressed) [*]	Yes	2 (25%)	0 (0%)	3 (30%)	2 (40%)
	No	4 (50%)	3 (100%)	5 (50%)	3 (60%)
	Not applicable	2 (25%) ^g	0 (0%)	2 (20%) ^g	0 (0%)
The caregiver-related outcome results should be discussed in the context of the other clinical trial outcomes	Yes	5 (62.5%)	2 (67%)	7 (70%)	2 (40%)
	No	3 (37.5%)	1 (33%)	3 (30%)	3 (60%)

Table 3. Continued

Is the caregiver-reported outcome the primary endpoint?		RCTs (N = 11)		Publications (N = 15)	
		Primary (N = 8)	Nonprimary (N = 3)	Primary (N = 10)	Nonprimary (N = 5)
Other information/protocol					
A copy of the instrument should be included if it has not been published previously	Yes	1 (12.5%)	1 (25%)	1 (10%)	1 (20%)
	No	6 (75%)	0 (0%)	8 (80%)	2 (40%)
	Not applicable	1 (12.5%) ^h	2 (50%) ^h	1 (10%) ^h	2 (40%) ^h

For descriptive purposes, subheadings of this table reflect that of reported in the International Society for Quality of Life Research (ISOQOL) recommended standards,¹⁹ however, rating of items was independent of location of the information within the manuscript.

^aThese are additional items to allow comparison to Dirven et al. (2014).¹⁶

Reasons for not applicable: ^aPsychometric evaluation; ^bDescriptive report; ^cQualitative interviews; ^dCross-sectional; ^eUnclear whether patients died during study; ^fFeasibility study; ^gNot addressed; ^hOnly published instruments used.

Synthesis of Findings From Trials Meeting Reporting Standards

Of the 11 unique RCTs, 9 (82%)^{23,25,26,30,32–34,37,38} satisfied $\geq 2/3$ of the key methodological criteria. These should therefore be considered of high reporting standard, enhancing the potential to influence clinical practice. Of these, 3 RCTs were described as definitive reports aimed primarily to enhance caregiver well-being.^{25,26,30}

These RCTs comprise complex and intensive neuro-oncology-specific interventions for caregivers, and demonstrate encouraging results in improving caregiver mastery, preparedness to care, and mental health. A protocolized program of up to six 1-hour face-to-face sessions with a psychologist, based on cognitive behavioral therapy and psychoeducation, covering issues commonly experienced by neuro-oncology caregivers, was compared to care as usual ($N = 56$).²⁵ Up to 8-month follow-up was recorded. Mental functioning stayed more stable in the intervention group, and caregiver mastery improved over time compared to the control group.²⁵ An 8-week, nurse-led, online needs-based intervention either delivered with or without access to a self-guided cognitive behavioral therapy for depression was compared to enhanced care as usual ($N = 120$).²⁶ The intervention group showed a statistically significant decrease in caregiving-specific distress as well as a trend toward improving mastery compared to the control group at 4 months.²⁶ A complex intervention including a telephone assessment of unmet carer needs, information materials, a home visit, and monthly telephone support for up to 12 months was delivered and compared to usual care ($N = 188$). Self-reported preparedness to care improved at 4 months with sustained effects up to a year.³⁰

However, not all RCTs with high reporting standards covering caregiver outcomes primarily aimed to enhance caregiver outcomes.³⁸ Furthermore, not all RCTs were reported as definitive trials.^{23,32–34} A pilot trial of meaning-centered psychotherapy for cancer caregivers ($N = 55$), delivered over 7 sessions and compared to enhanced care as usual, demonstrated preliminary efficacy in enhancing a sense of personal meaning and existential transcendence (primary endpoint), as well as enhanced spiritual well-being and sense of faith (secondary endpoints).²³ Effects observed

were sustained up to 2 months postintervention.²³ A small-scale study with 20 patient and caregiver participants randomized to either 12 sessions of dyadic yoga or a waitlist control group, found evidence of reduced depressive symptoms, fatigue, and better mental quality of life in caregivers in the intervention group.³² A more recent 3-arm pilot RCT from the same team comparing 15 sessions of dyadic yoga, 15 sessions of individual caregiver yoga, and usual care ($N = 67$) found better outcomes in the individual yoga arm than the dyadic yoga arm or usual care. With follow-up conducted up to 12 weeks, benefits reported included improved mental quality of life, enhanced caregiver esteem, less health decline, and less financial burden.³³ Another pilot RCT from the same group compared a group of patients and caregivers receiving 4 weekly therapist-led meditation sessions delivered via videocall ($N = 35$), but found no beneficial effects for caregivers.³⁴ A pilot RCT of an electronic social network intervention offered to caregivers and compared to care as usual ($N = 40$), with follow-up until 6 weeks, showed some preliminary efficacy for reducing caregiver depressive symptoms, but not anxiety or burden.³⁷

Discussion

Neuro-oncology caregiver research is a growing and developing field. It is widely acknowledged that caregivers have specific and concerning unmet needs throughout the patient's disease trajectory (and beyond), with few available support options and even fewer supported by solid scientific evidence of effectiveness. Good-quality RCTs can help persuade policymakers and healthcare insurers of the positive impact of adequately supporting caregivers. Specifically looking at adult neuro-oncology caregiver and patient populations, we were able to identify 15 publications of 11 RCTs that included caregiver outcomes with low overall risk of bias. These were assessed against a 33-item checklist (23 items for secondary analysis reports), based on the ISOQOL criteria for PRO reporting. In general, the quality of methodological reporting was high, with 9 out of 11 RCT reports satisfying $\geq 2/3$ of the assessed criteria. This



Figure 2. Risk of bias assessment for each randomized controlled trial.

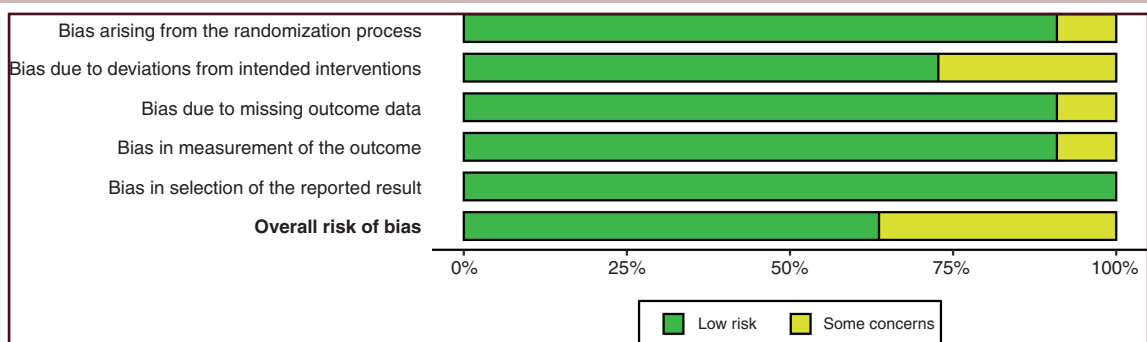


Figure 3. Summary of risk of bias across randomized controlled trials.

signals that these trials would be of high enough reporting standards to impact clinical practice. Yet, only 3 RCTs were definitive trials aimed at supporting caregivers,^{25,26,30} with 5 reported as pilot or feasibility studies.^{23,32–34} In addition, one definitive trial collected caregiver outcomes but did not aim to enhance caregiver well-being.¹¹ Previous reviews have similarly concluded that the certainty of evidence for the effectiveness of neuro-oncology caregiver support interventions is low,^{11,12} underscoring the importance of further, high-quality trials. In studies of

other patient-caregiver populations such as stroke³⁹ and Parkinson's disease,⁴⁰ risk of bias can be variable, which has also been linked to incomplete description and reporting standards—although to our knowledge, a detailed assessment of RCT publications along reporting criteria has not been undertaken.

The ISOQOL criteria were used for consistency with a previous systematic review performed in neuro-oncology patient RCTs,¹⁶ but we note that these were not specifically designed for nondefinitive trials. The distinction between

definitive trials and pilot or feasibility trials was based on how this was presented within each publication and may not be clear-cut. Following the definitions of Eldridge et al.,⁴¹ feasibility studies determine whether something can be done; in a pilot study, a (part of) future trial is conducted on a smaller scale; and a definitive trial is used to assess the effect of an intervention. Therefore, if the goal is to ascertain effects, it would be advisable not to present findings using the terms pilot or feasibility trial. Linked to this, definitive trials should be adequately powered to detect effects on primary outcomes; an inadequately powered definitive trial should not be presented as a pilot or feasibility study. While reporting standards of included publications were already high, we noted opportunities for improvement, specifically related to reporting of sample size calculations, details on statistical approaches, and adequate discussion of limitations and clinical significance of the study. In addition, research teams should aim to provide copies of any nonvalidated caregiver outcomes used. A previous systematic review of 157 publications covering 120 studies on adult neuro-oncology caregivers highlighted the breadth of constructs assessed with a great variety of outcome measures—with only 17 questionnaires used in more than 2 studies to assess the same construct.¹³ In the absence of clear consensus on core outcome measures in neuro-oncology caregiver studies, the use of study-specific questionnaires will likely remain common, underscoring the need to supply these as supplemental material alongside publications.

There were 3 definitive RCTs that met our predefined threshold of high-quality reporting standards and should therefore be of sufficient standard to impact clinical practice.^{25,26,30} These 3 trials entailed differing complex psychosocial support interventions with a heavy psychoeducation component, delivered in a variety of ways (online, telephone, face-to-face). All point toward improved self-efficacy-related outcomes (mastery, preparedness to care) as well as enhanced mental functioning. The pilot or feasibility RCTs included in the current effort provide further preliminary evidence for the effectiveness of meaning-centered psychotherapy, yoga, and an electronic social network intervention in improving caregiver outcomes.^{23,32–34,37} These results are in line with previous systematic reviews, which similarly conclude that there is preliminary evidence of effectiveness of neuro-oncology caregiver support interventions but that the certainty of evidence is still low.^{11,12} Of note, a search update performed in July '24 identified 3 additional reports of trials we already included (Care-IS^{42,43}; SmartCare⁴⁴) and 2 new RCTs with interventions targeting people with primary brain tumors and their caregivers—one covering the remote delivery of a psychological support needs intervention (Tele-MAST)⁴⁵ and the other a dependent care theory-based postsurgical home care intervention.⁴⁶ Inclusion of these studies in the present review would not alter results or conclusions significantly. Strengths of the current report lie in its systematic review approach and linkage to previous efforts in determining reporting standards in (neuro-) oncology studies.^{16,19} Our rather inclusive eligibility criteria for publications can be seen as a limitation, as not all study designs and aims lend themselves readily to assessment against the predefined criteria (eg, qualitative reports linked to

RCTs). It should also be noted that our study team has also contributed to many of the publications included in this review. To limit potential bias in scoring criteria, all publications were scored by at least 2 team members (who did not author the publications they scored), with a final check performed by the lead author. Finally, the distinction between pilot studies, feasibility studies, and definitive trials was not clear-cut, with indeed one definitive trial²⁵ having a smaller sample size than several pilot/feasibility studies.

This first report from the RANO-Cares working group demonstrates that reporting standards are high in the field of neuro-oncology caregiving, but we also note several specific reporting areas (sample size; statistical approaches; clinical implications and limitations; transparency related to nonvalidated outcome measures) that can be improved upon. The RANO-Cares group further aims to undertake efforts to assess key constructs and measurement tools specific to neuro-oncology caregiver research. Ultimately, and in collaboration with other initiatives such as the International Neuro-oncology Caregiver Consortium, we envisage that this aids to improve the chances of evidence-based supportive interventions becoming widely available to neuro-oncology caregivers.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Practice* (<https://academic.oup.com/nop/>)

Conflict of interest statement

F.W.B.: MedScape (speaker). K.P.: Servier (speaker and part of the Global Glioma Education Steering Committee). D.C.: Consultant for Guidepoint Global LLC, Dedham Group, Gerson Lehrman Group, and Putnam Associates. T.W.: Advisory Board for Alexion, AnHeart, Servier; Consultant Novocure.

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