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Angaben zur Veröffentlichung / Publication details:

Schildmann, Eva, and Irene J. Higginson. 2011. "Evaluating psycho-educational interventions for informal carers of patients receiving cancer care or palliative care: strengths and limitations of different study designs." *Palliative Medicine* 25 (4): 345–56. https://doi.org/10.1177/0269216310389223.

Original Article

PALLIATIVE MEDICINE

Palliative Medicine
25(4) 345–356

DOI: 10.1177/0269216310389223
pmj.sagepub.com
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Evaluating psycho-educational interventions for informal carers of patients receiving cancer care or palliative care: Strengths and limitations of different study designs

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Abstract

Despite evidence of negative psychological sequelae and unmet needs, there are few evaluated interventions for informal caregivers in cancer and palliative care. The aim of this article is to debate the strengths and limitations of randomized controlled trials (RCTs) and other designs that can be used to evaluate the effectiveness of these interventions. Psycho-educational interventions are used as example for this debate article, as a number of studies of various designs evaluating this type of intervention have been published. Systematic searching in Medline and the bibliography of a relevant systematic review identified five RCTs, one pre-test/post-test study with a control group and six one-group pre-test/post-test studies of psycho-educational interventions for caregivers. The methodological strengths and weaknesses were assessed. RCTs are seen as the gold standard, but can have important limitations in the context of carer intervention research, including biased recruitment and low generalizability, problems with blinding and attrition. Pre-test/post-test studies with a control group may be more feasible and more generalizable. Their crucial limitation is selection bias. Before–after studies are compromised by additional specific biases and therefore are the weakest of all discussed designs. After analysing the strengths and weaknesses of the mentioned study designs, this paper presents strategies to address the limitations of RCTs evaluating psycho-educational interventions for carers in cancer or palliative care.

Keywords

Caregivers, clinical trials as topic, evaluation studies, intervention studies, palliative care, research design

Background

Informal carers, who may or may not be family members, have been defined as 'lay people in a close supportive role who share in the illness experience of the patient and who undertake vital work and emotion management'.[1] Carers of patients receiving cancer care or palliative care have been shown to have high levels of anxiety, depression and strain, as well as unmet needs for information and both psychological and practical support.[2] There is no consensus on how to meet those needs, as evaluated interventions for these carers are rare.[2,3] It has been argued that the most feasible, appropriate and rigorous designs for such intervention studies are yet to be identified.[4] The aim of this article is to debate the strengths and limitations of randomized controlled trials (RCT) and other designs to evaluate the effectiveness of interventions for

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informal carers of patients receiving cancer care or palliative care. Psycho-educational interventions are used as example for this debate article, as a number of studies of various designs evaluating this type of intervention have been published. Psycho-educational interventions are defined as 'a structured programme geared toward providing information about the care receiver's disease process and about resources and services and training caregivers to respond effectively to disease-related problems (...). Support may be part of a psycho-educational group, but it is secondary to the educational content'.[5] This review considers interventions in a group or individual format.

Methods

Search strategy

Studies for this debate article were identified in a systematic search in Medline via Ovid, 1950 to July 2009, and the bibliography of a relevant systematic review.[3] Search terms were the following: (palliative care OR terminal care OR hospices OR hospice care OR terminally ill OR end of life) AND (caregivers OR carers OR family) AND (intervention studies OR evaluation OR evaluation studies as topic OR clinical trials as topic OR clinical trial OR randomized controlled trials as topic OR randomized controlled trial OR treatment outcome OR random allocation OR effectiveness OR efficacy) AND (education OR health education OR education, nonprofessional OR patient education as topic OR psycho-education$ OR intervention), using both key words and medical subject heading (MeSH) terms, if possible.

Inclusion and exclusion criteria

In analogy to the systematic literature review of carer interventions and their effectiveness by Harding and Higginson,[3] papers that reported evaluation results of the effectiveness of interventions for adults actively providing informal care for non-institutionalized patients with cancer (who were not receiving palliative care) and palliative care patients were included. Additional inclusion criteria for this debate article were the fulfilment of the above given definition of psycho-educational intervention and publication in English. Lack of data on effectiveness of the intervention measured by carer-related outcomes was an exclusion criterion.

Evaluation studies

Evaluation studies of palliative care services, such as interventions for carers, are regarded almost entirely as so-called pragmatic trials that investigate effectiveness (whether the intervention works in real-life practice conditions) as opposed to efficacy (whether it works under ideal conditions).[6,7,8] Trials studying effectiveness can be experimental, quasi-experimental or observational (see Table 1).[6,9] All evaluations of the effectiveness of psycho-educational interventions for carers are experimental or quasi-experimental, as there is always 'artificial manipulation of the study factor' in the form of planning and introducing the intervention. Therefore, observational studies are not discussed in this paper.

Randomized controlled trials

RCTs have been referred to as the gold standard for evaluating interventions in healthcare.[10,11] The search in Medline and the bibliography of a relevant systematic review[3] identified five parallel group RCTs evaluating the effectiveness of psycho-educational interventions for carers in palliative or cancer care (see Table 2). The strengths and limitations encountered in these studies will be discussed in the following.

Strengths

Randomization is the only allocation method that can, if appropriately used and sample size is large enough, protect the study by the risk of selection bias, as it should distribute all confounding variables approximately equally between the groups.[8,11] In the RCTs evaluating psycho-educational interventions, this is demonstrated for known potential confounding

Table 1. Types of epidemiological study designs

Type of study	Artificial manipulation of the study factor	Randomization	Examples of study designs
Observational	No	No	Cross-sectional, case-control, cohort study
Quasi-experimental	Yes	No	Before–after study, pre-test/post-test with control group study
Experimental	Yes	Yes	RCT

RCT = randomized controlled trial.
Source: Amended table from Costantini and Higginson.[9]

Table 2. Characteristics of the five RCTs and the pre-test/post-test study with control group evaluating psycho-educational interventions for carers of cancer or palliative care patients

1st author	Heinrich[12]	Toseland[14]	Hudson[16]	Walsh[15]	McMillan[13]	Harding[4]
Design	RCT, 2 sites	RCT, 1 site	RCT, 2 sites	RCT, 7 sites	RCT (3 arms), 1 site	Pre-test/post-test design with control group, 2 sites
Carer population (characteristics of care recipients)	Cancer patients [a](not receiving palliative care)	Cancer patients [b](not receiving palliative care)	Cancer patients receiving home palliative care	Cancer patients receiving home palliative care	Cancer patients receiving home palliative care	Patients receiving home palliative care
Recruitment (participants/all eligible carers)	Not reported for carers, but 'problematic'	27%	30%	76%	'Difficult', not completely clear: 480 subjects 'sought', 329 randomized/ 354 eligible = 93%?	43% [d]
Reasons for non-participation of carers	Work during time scheduled for groups or evaluations	No interest (55%), distance problem (27%), not enough time (15%), dislike research projects (3%)	Not reported	'Refusal of visit of research assistant or no consent to study', reasons not reported	Patient or carer failed the initial screening, no other reasons reported	Reasons for not choosing intervention: no interest ($n = 15$), cannot make afternoons ($n = 13$), time commitments ($n = 7$), lack of identification with carer role ($n = 1$), poor personal health ($n = 1$)
Sample size	25[c]	86	106	271	329	73
Length of intervention period	6 weeks	Not clear, about 6 weeks	About 2 weeks	6 weeks	1–1.5 weeks	6 weeks
Type of intervention	Group	Individual	Individual	Individual	Individual	Group
Time between baseline and last follow-up	5.5 months	Not clear, about 2 months	Until 2 months after death of patient	3 months (+ one follow-up 4 months after death of patient)	4 weeks	5 months
Inclusion criteria regarding estimated survival time or performance state of patient	Karnofsky performance status ≥ 70	ECOG 1 - 3	ECOG 0 – 3	Exclusion if 'patient unlikely to survive the time it would take to introduce the intervention'	Exclusion if 'patient performance status suggested that patients would not survive more than a few days'	≥ 3 weeks

(continued)

Table 2. Continued

1st author	Heinrich[12]	Toseland[14]	Hudson[16]	Walsh[15]	McMillan[13]	Harding[4]
Carers whose patient died before the follow-up excluded from main analysis?	Not stated	Apparently yes, as death stated as reason for attrition	Not stated	Yes	No, but no further data collected	Not stated
Attrition (carers not providing data/all included carers)	11% (not clear if at 3.5 or at 5.5 months after baseline)	9% at about 2 months after baseline	29% at 5 weeks after baseline, 58% at 8 weeks after death of patient	32% at 4 weeks, 50% at 9 weeks, 55% at 12 weeks after baseline 18% 4 months after death of the patient	55% at 2 weeks 69% at 4 weeks after baseline	44% at 8 weeks, 64% at 5 months after baseline
Reasons for drop-out	'Attrition due to illness prevented analysis of the final, 4-month follow-up data'	Distance and transportation problems, no pressing problems with which they needed help, deteriorating health and death of patient	Not given in the original paper	Drop-out due to death of the patient: 16% of all patients had died at 4 weeks, 31% at 9 weeks, 40% at 12 weeks, reasons for drop-out other than death not reported	Patient decline (29%), patient death (21%), caregiver feeling overwhelmed ('largely associated with patients' worsening condition') (23%), other reasons not reported	Not reported
Effect of intervention shown	On some outcome variables	Only in a distressed subsample	On one outcome variable	None	On some outcome variables	None

Percentages for this table are taken from the original papers or calculated from the original data.

[a]'ambulatory cancer patients with incurable cancers or uncertain prognoses', not further specified in the original paper.

[b]Stage of cancer between initial diagnosis and treatment and terminal illness (exclusion criteria: diagnosis of cancer within the previous three months, carers of patients with an ECOG score of 4 (because the authors wanted to 'focus on patient and caregiver coping prior to the terminal phase of illness').

[c]Also includes 51 patients, all data reported in this table only refer to the carers.

[d]Uptake of intervention (carers accepting the intervention/all eligible carers) = 25%.

variables, as there were no significant differences between the groups in demographic characteristics and other baseline variables of patients or carers.[12–15] As indicated by some imbalances in baseline carer strain and quality of life between the intervention and the control group in one of the RCTs,[15] randomization does not guarantee that the groups are identical, even in large samples. However, it ensures that the distribution of known and unknown confounders in the groups is determined by chance alone.[11] If they are distributed approximately equally, any difference in outcome can be attributed to the intervention – provided there are no other biases or limitations as discussed in the following.[7]

The effectiveness and safety of psycho-educational interventions for carers is not sufficiently proven. Therefore, there is equipoise as a requirement for ethically justified randomization, that is, uncertainty whether the new intervention is superior to standard care.[8]

Limitations

Low recruitment and small sample size, meaning low power to detect any intervention effects, was a prominent limitation of the discussed RCTs evaluating psycho-educational interventions for carers. Except the multicentre RCT,[15] all RCTs – whether they were conducted in cancer care or in palliative care populations – reported recruitment problems, with recruitment percentages of around 30% of all eligible carers[12–14,16] (see Table 2). Reasons for not participating were documented in the two RCTs conducted with carers of cancer patients not receiving palliative care; in the group intervention trial, work during the time scheduled for groups or evaluations was given as reason for non-participation.[12] In the study evaluating an individual-based intervention in cancer care, 55% of the non-participating carers stated 'not interested in participating' as the reason for non-participation, 27% 'distance from the medical oncology center', 15% 'not enough time to participate 'and 3% 'dislike research projects'.[14] The three RCTs conducted in palliative care populations did not provide data regarding the reasons for non-participation.[13,15,16]

Differences in baseline characteristics between participants and non-participants were not tested for in any RCT. Therefore, the strength and direction of *bias in participant selection* cannot be assessed.[17] *Biased participant recruitment* reduces the *external validity, that is, generalizability* of a study.[17] In RCTs, it can be due to objections against randomization or specific wishes about further care by carers or professionals, for example, no interest in the carer intervention.[17] Unfortunately, there are no specific data provided to demonstrate the impact of these factors on trial participation in the discussed five RCTs. As stated above, in one of the RCTs evaluating psycho-educational interventions for carers, 55% of the eligible carers who did not participate gave 'not interested in participating' as reason for non-participation.[14] From the original paper, it is not clear whether this was a lack of interest in study participation in general – potentially partly due to objections against randomization – or a lack of interest in the offered intervention. That the latter could be an important factor could be postulated based on the results of the pre-test/post-test study with a control group discussed below. The commonest reason given for not taking up the intervention and choosing the control arm instead was not being interested in the intervention.[4] One RCT found that the carers included in the study were highly functioning, and discussed *professional gatekeeping* as potential causative factor for the recruitment of well-adapted carers and exclusion of those who were less well functioning.[16] However, there are no other data to confirm this hypothesis of professional gatekeeping as a cause for biased recruitment in this trial.

All five RCTs only included carers of cancer patients (see Table 2).[12–16] Therefore, their results cannot necessarily be generalized to carers of patients with a non-cancer diagnosis.

Limitations regarding the randomization procedure and blinding were reported in the trial evaluating a group intervention. Consecutive participants were 'enrolled in the group condition that was currently open', because the subject pool was small and subjects had to begin the intervention concurrently.[12] This allocation was not really random and was not concealed. *Blinding* of data collectors was not done in this and another RCT.[12,16] Blinding of participants is virtually impossible due to the nature of the studied intervention, and consequently was not done in any RCT. This introduces *measurement bias*, probably overestimating the effects of the intervention. *Choosing an appropriate control* to compare with the intervention arm is also problematic in RCTs evaluating the effectiveness of psycho-educational interventions for carers. If 'standard care' is used as the control arm, the potential 'active component' of the intervention cannot be differentiated from the effects of the 'time away from caring' or the extra time and attention given to carers in the intervention arm. One of the RCTs, therefore, introduced standard care plus supportive visits as a third trial arm;[13] the others did not address this problem.

Attrition is a well-known limitation of palliative care trials[17] and was a significant factor decreasing numbers for analysis and therefore power to detect any effects, particularly in the RCTs evaluating psycho-educational

interventions for carers in palliative care populations (see Table 2).[13,15,16] It has been argued that randomization for participative interventions, such as psycho-educational interventions, will cause disappointment of those carers who are randomized to the non-preferred arm, leading to higher attrition.[18,19] There are no data available from the five RCTs to support or dismiss this hypothesis. Three RCTs failed to assess *differences in attrition* between the study groups,[12,14,16] although such differences would introduce *selection bias*. The other two RCTs did not find differential attrition in the study arms.[13,15]

Reduction of the contrast between the intervention and the control, for example by unforeseen cointerventions, unequally distributed between the groups, was another problem encountered in the RCTs evaluating psycho-educational interventions. In one of them, for example, over 20% of the control group received some form of counselling or attended support groups, whereas the intervention group did not.[14] The nurses of the carers in the standard care arm being aware of the trial and trying harder to provide carer support has been discussed to be another potential factor that reduces the contrast between the intervention and control groups,[15,17] without data from the studies to support or dismiss this hypothesis.

Choosing specific, reliable, sensitive and appropriate outcome measures that are *validated also for carers of palliative care patients* was a problem common to all study designs. Although there are some data on reliability and validity of carer outcome measures also in palliative care populations, it is widely acknowledged that further validation in palliative care contexts is required.[20–22] As this is a methodological problem that is not directly linked to the choice of the study design, which is the focus of this paper, but is a limitation common to all discussed studies independent of their design, it is not further discussed here.

Quasi-experimental studies

It has been argued that the discussed challenges, which are encountered in most palliative care RCTs, lead to a serious compromise of RCT quality and a lack of clear evidence, and that other designs may yield more useful evaluation data.[7,9,23] One alternative are quasi-experimental studies. These are non-randomized studies in which the intervention is introduced to observe its effect (see Table 1).[9] There is a variety of designs of quasi-experimental studies.[9] Two types have been used in published evaluations of psycho-educational interventions for carers: the pre-test/post-test design with a control group and the one-group pre-test/post-test design.

Pre-test/post-test studies with a control group

The search in Medline and the bibliography of a relevant systematic review[3] identified one study with this design evaluating a psycho-educational intervention for carers in palliative care (see Table 2).[4] In this study, allocation to the intervention was by means of self-selection.

Strengths

The strength of this design is its experimental character without randomization,[9] thereby *avoiding the potential problems of randomization*. The study by Harding et al.[4] may be said to be *more generalizable* than RCTs,[4,24] because it includes the carers who decline the intervention and would therefore not consent to a RCT. Another reason for greater generalizability than the RCTs discussed above is that it included carers of all palliative care patients, not only cancer patients.[4] A further strength is that it *explores carers' preferences* and reasons for these preferences as important factors in participative interventions. For example, reasons for not taking up the offered psycho-educational intervention given by the carers were lack of interest, that they would like to attend but could not make afternoons, that they would not leave the patient or had pressurized time commitments, 'I'm not a carer' and poor personal health.[4] These data can help to make future interventions of this kind more acceptable to carers.[18]

Recruitment may be higher than in RCTs, as gatekeeping by professionals and refusal by carers due to objection against randomization or the tested intervention is avoided. The disappointment of carers who strongly wished to receive the intervention but were randomized to the control arm in a RCT is also prevented.[3] This may *reduce the attrition* associated with that disappointment.[18,19] However, the studies compared in this article do not support these assumptions: The recruited proportion of eligible carers in the quasi-experimental study was not higher than in the RCTs (see Table 2). Global attrition is difficult to compare due to the differences in study populations and length of follow-up and consequent differences in drop-out due to patients' death. However, death was the main reason for attrition,[13,15] and attrition does not seem to be lower in the quasi-experimental study than in the RCTs in palliative care populations (see Table 2).

One might argue that the risk of professionals trying to compensate for the perceived 'worse care' for the control group is less in trials with self-selection of the study arm. Similarly, it could be assumed that carers who chose the control treatment in a quasi-experimental study are less likely to seek any support similar to the

tested intervention during the study period. Therefore, the *contrast between the groups* may be easier to maintain in this study design than in a RCT, making it more likely to detect an intervention effect. The study by Harding et al.,[4] however, did not demonstrate an effect of the intervention on psychological scores of the carers.

Finally, this design is *more feasible* and probably *less expensive and time-consuming* than a RCT. However, there are no data provided in the discussed studies to illustrate this.

Limitations

The crucial limitation of this design is the *selection bias* inherent in all non-randomized studies. This is of particular importance when allocation is by self-selection, as people who choose the intervention are likely to be different to those who choose the control in characteristics related to the outcome under study.[9] In the non-randomized controlled study evaluating a psycho-educational intervention, carers who declined the intervention felt more burdened and were caring for less well patients than the carers accepting the intervention.[4] There will most likely be systematic differences between these groups in their trajectories without intervention and their potential responsiveness to it, which could underestimate, but also overestimate, its effects.[9] Multivariate analysis, stratification for relevant characteristics or propensity analysis can partly account for the lack of baseline equivalence between the groups.[4,11] However, it can only control for measured factors, and there will always be unknown and unmeasured confounding variables. In addition, insufficient sample size precludes multivariate analysis or stratification, which was the case in the non-randomized controlled study evaluating a psycho-educational intervention.[4] The fact that attrition was different in the two groups introduced additional selection bias.[9]

One-group pre-test/post-test design (before–after studies)

These studies have two measurement points: one before and one after the intervention (therefore also called before–after studies), and no control group. The systematic search in Medline and the bibliography of a relevant systematic review[3] identified six before–after studies evaluating the effectiveness of psycho-educational interventions for carers in cancer and palliative care (see Table 3).[25–30]

Strengths

Their strength in comparison with a RCT is, as for the just-discussed non-randomized controlled study, their experimental character without randomization, allowing one to *include all interested individuals in the intervention group*.[31] This could possibly *increase recruitment* and *reduce attrition*. However, as far as can be judged from the numbers reported in the before–after studies, they did not encounter less problems with recruitment and/or attrition than the RCTs, and reasons for low recruitment and attrition were similar as in the RCTs (see Table 3).[25,26,28,30] Another strength of a before–after study is that it is *more feasible* and *considerably less expensive and time consuming* than a RCT or a non-randomized controlled study.[31] Unfortunately, this cannot be illustrated by the studies discussed in this paper, as they have not reported any data regarding requirements of time and resources.

Limitations

The internal validity of this design is compromised by the fact that there is no possibility of trying to adjust for or understand selection bias, as discussed above. In addition, there are some methodological problems specific to this design; a change over a period of time as a general development independently from the intervention, which could itself explain the change in the measured outcomes, is called *secular (or temporal) trends*.[32] The lack of a control group makes it impossible to exclude secular trends as the cause of effect found in the study.[31] One of the RCTs, for example, found improvements in psychosocial adjustment over time in both the experimental and the control group.[12] A before–after study evaluating the same intervention would have wrongly attributed this change to the intervention. Secular trends have been discussed as a possible cause for the observed effect of the intervention in one of the six before–after studies evaluating psycho-educational interventions for carers.[30]

The second specific limitation of before–after studies relates to *regression to the mean*, that is, the tendency of individuals at the extreme to have values nearer to the mean of the general population on repeated measurements.[32] This cannot be excluded as a possible explanation of any effect found in a non-controlled study with only two measurements for each individual.[31] However, it has not been discussed as a limitation in any of the six before–after studies. Due to these limitations, this is by far the weakest of the discussed designs, and results need to be interpreted very cautiously, taking into account these limitations and biases.

Strategies to address the discussed limitations of the different study designs

A strategy to address the problem of secular trends in before–after studies evaluating carer interventions

Table 3. Characteristics of the six one-group pre-test/post-test studies (before–after studies) evaluating psycho-educational interventions for carers of cancer or palliative care patients

1st author	Robinson[29]	Pasacreta[28]	Cameron[30]	Kwak[26]	White[27]	Hudson[25]
Carer population (characteristics of care recipients)	Cancer patients (not further specified)	Cancer patients (not further specified)	Patients with advanced cancer (3–6-month survival prognosis)	Patients 'during the last years of life' (not further specified)	Patients with 'a life-threatening illness' (not further specified)	Patients requiring palliative care because of malignant disease
Recruitment (participants/all eligible carers)	Not reported	'Major problem', no numbers	44%	Not reported	Not reported	44%
Reasons for non-participation of carers	–	Employment, family obligations, fear of leaving the patient alone, physical restrictions of the caregiver	No consent, patient died before intervention, not coming back to hospital for intervention	–	–	Caregiver coping and supported ($n = 17$), not interested ($n = 14$), working ($n = 10$), relative too unwell to leave alone ($n = 9$)
Sample size	Not reported	504	58	2025	205	74
Length of intervention period	? (6 hours in 1, 2, 3 or more sessions)	? (3 sessions)	1 hour	about 4 sessions over 'a few weeks'	? (3–6 sessions)	3 weeks
Type of intervention	Group	Group	Individual	Group	Group	Group
Time between baseline and follow-up	About 8 weeks?	About 4 months?	4 weeks	'a few weeks'	About 7 weeks?	5 weeks
Attrition (carers not providing data at baseline AND follow-up/all included carers)	Not reported	63%	41%	46%	Not reported	41%
Reasons for not completing intervention/ not providing data at follow-up	–	Concern of facilitators about 'response burden'	Unable to come to hospital ($n = 11$), patients died before follow-up ($n = 4$), lost to follow-up ($n = 2$)	Not reported	Unstable nature of the patient's illness, sudden deteriorations, find someone to care in the carer's absence, hospitalization, having a 'bad day'	Not reported
Effect of intervention shown	Yes	On some outcomes	Yes	Yes	Yes	On some outcomes

would be the minimization of the duration of follow-up after the carer intervention.[31] The problem of regression to the mean in before–after studies is reduced by including more measurement points, producing a time series study, for example with an additional measurement point during the intervention period.[31]

Strategies for improvement of non-randomized controlled studies include aiming for greater participant numbers, which allow multivariate analysis to account for the lack of baseline equivalence in non-randomized studies.[4]

Strategies to address the discussed limitations of RCTs evaluating the effectiveness of interventions for carers – which can partly also be used to address limitations of the other discussed study designs – are presented in Table 4 and summarized in the following. Recruitment problems can be addressed by multisite trials, hiring a trained research assistant for recruitment, ensuring optimal support by the clinical team, for example by repeated personal information to them, and providing respite for the intervention sessions and transport for the carers.[4,13–16] Strategies to

Table 4. Strategies for improving the external and internal validity of RCTs to evaluate carer interventions in palliative care. (This table contains suggestions from Rinck et al.[17] and Jordhoy et al.[36] and the references indicated.)

Methodological problem	Effect on study quality	Strategies for improvement
Low recruitment numbers, e.g. due to gatekeeping, refusal of carer because of opposition to research in general or to randomization or specific wishes about further care	Reduced power to detect effects	Trained research assistant for recruitment,[13] ensure optimal support of entire team caring for the patients and carers, e.g. by repeated and personal information to them,[14] simple referral routines that minimize workload for team, reduce gatekeeping (see below), multisite trial (with appropriate measures to standardize intervention, see below),[14–16] respite during intervention times to enable carers to attend intervention sessions,[13] transport for carers[4] If possible, partially randomized participant-preference trial[33] or 'fast track' RCT[35]
Biased recruitment, e.g. due to gatekeeping, refusal of carer because of opposition to research in general or to randomization or specific wishes about further care	Reduced external validity/ generalizability	Reduce gatekeeping (see below), report numbers of non-participants (non-eligible and eligible 'refusers') and collect baseline data on at least some key characteristics on them to explore extent and direction of bias;[14] record reasons for non-participation[4,14] If possible, partially randomized participant-preference trial[33] or 'fast track' RCT[35]
Gatekeeping by professionals (e.g. due to aversion against randomization or the belief that trials are intrusive or inappropriate)	Reduced and biased recruitment (see above)	Information for professionals (see above), screening for eligibility by research staff, not team caring for the patient;[13] at least record the status of all carers in relation to the inclusion criteria[4]
Problem with randomization procedure for group intervention	Possible selection bias	Block randomization + mask referring professionals to block size[15]
Groups differing regarding possible confounding variables, especially if small numbers are being randomly allocated	Selection bias	Adequate randomization procedure; if appropriate, stratified random allocation (separate subjects into different subgroups (= strata) based on key risk factors, and randomly allocate them within each stratum);[32] multivariate analysis to adjust for baseline values[4]
Blinding of participants impossible	Measurement bias	No solution to that, but at least blind data collector[13,14]
Attrition (loss to follow-up e.g. due to death of the patient or failure to return questionnaires)	Reduced power to detect effects Selection bias, if different between trial arms	Allow for considerable attrition in sample size calculation, allow for overoptimistic prognostication when setting the limit for life expectancy of patient as inclusion criterion, make use of prognostic factors such as performance status,[14,16] shorter length of intervention/follow-up,[13] additional data collection at midpoint during the intervention period,[4,15] minimize number of questionnaires etc.

(continued)

Table 4. Continued

Methodological problem	Effect on study quality	Strategies for improvement
		Specify reasons for attrition (i.e. how many patients died, how many carers failed to provide data) and the corresponding numbers per group,[15] assess differences in attrition between the study groups,[13,15] intention-to-treat analysis
Standardization of intervention (especially for multisite trials)		Clear protocols, training and regular supervision of staff [4]
Difficulty to choose adequate control intervention	If 'standard care': potential confounding effect of just 'time away from caring' or extra time and attention given to carers in intervention arm cannot be differentiated from putative 'active component' of the intervention	Three arms – design, e.g. comparing (1) standard hospice care alone with (2) standard hospice care plus three intervention visits and (3) standard hospice care plus three supportive visits[13]
Choice of inappropriate outcomes and outcome measures	Reduced internal validity Failure to detect effect if measure is not sensitive to change	Use outcome measures that are specific to the intervention, reliable, validated for palliative care, sensitive to change and appropriate (pilot them, more research into carer outcome measures in palliative care) Include qualitative data to help interpret quantitative results[4,15]
Reduced contrast between intervention and control	Reduced power to detect effects	Explicitly describe the intervention and the contrast between intervention and control Document the care actually given including cointerventions[14] Intention-to-treat analysis
Inadequate timing of outcome measurements	Failure to detect effect Potentially higher attrition (see above)	e.g. data collection at midpoint of group intervention (possibly these interventions are mainly beneficial while the intervention is ongoing?)[4,15] Discuss the validity of the results, taking into account the extent and direction of biases and confounding variables[31]

reduce gatekeeping by professionals as a cause of reduced and biased recruitment include information to them and screening for eligibility by research staff.[13] Key variables of non-participants and participants should be collected and compared at baseline to assess extent and direction of selection bias.[4,14] Randomization problems for group interventions requiring individuals to start the intervention together can be addressed by block randomization and masking of the referring professionals to the block size.[15] Baseline differences between the groups – for example when small numbers are being randomly allocated – can be adjusted for by multivariate analysis.[4] The problem that blinding of the participants is impossible in studies of participative carer interventions cannot be solved, but blinding of data collectors can at least prevent even greater measurement bias.[13,14] Standard care plus supportive visits can be used as a control arm to account for the problem that time away from caring or extra attention to carers in the intervention arm cannot be differentiated from effects of the 'active intervention component' when using standard care alone as control arm.[13] Strategies to reduce attrition in studies evaluating carer interventions include the reduction of the duration of the intervention and the follow-up period.[13] A shorter follow-up and data collection points during the intervention have also been recommended, as, potentially, the main effect of the intervention is to be shown during the intervention, not after withdrawal of the 'agent of change'.[4,15]

An alternative to a 'classic' RCT could be a partially randomized patient-preference trial. This allows participants with treatment preferences their desired treatment and only randomizes those without strong preferences.[18] It therefore recruits participants who would not have been recruited to a RCT, providing

greater generalizability.[33] However, its feasibility in the context of carer intervention studies remains to be tested, as sufficient numbers in the randomized arms and overall a larger sample are needed.[18,33,34]

Another alternative to a 'classic' RCT is a 'fast-track' RCT. In the latter, participants are randomized to receive either the intervention immediately ('fast track') or usual best practice alone (control) for a certain time period, after which they are offered the intervention.[35] This design has been shown to achieve better recruitment than most palliative care trials in a study evaluating the cost effectiveness of a palliative care service in Multiple Sclerosis.[35] Its seems worth testing its usefulness in the evaluation of carer interventions.

Conclusion

Evaluation of interventions for carers is challenging, partly because of general problems of research in palliative care[7] and partly because these are complex interventions. The choice of the study design to evaluate an intervention for carers has to be based on considering and balancing the feasibility, internal validity and generalizability of the methodological options.[9] While it has been argued that a well-designed quasi-experimental study can have higher internal validity than a RCT with many limitations,[9] the non-randomized controlled study analysed in this review did not encounter fewer problems than the RCTs regarding recruitment and differential attrition. Its inherent selection bias compromises internal validity additionally. The before–after studies have additional specific limitations and therefore produce by far the least valid results of all discussed designs. A well-designed RCT possesses the highest internal validity. Strategies to address the limitations encountered in the reviewed RCTs evaluating carer interventions have been discussed. Partially randomized patient-preference trials and 'fast-track' RCTs are alternatives to 'classic' RCTs. Their feasibility and usefulness in evaluating the effectiveness of carer interventions should be tested in future trials.

Acknowledgement

This paper is based on an assignment for the Master's of Science course in Palliative Care at King's College London.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

The authors declare that they have no competing interests.

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