



Cost-effectiveness of a specialist palliative care nurse-patient consultation followed by an interprofessional case conference for patients with non-oncological palliative care needs: results of the KOPAL trial[✳]

Sophie Gottschalk^{1^}, Hans-Helmut König¹, Tina Mallon², Josefine Schulze², Jan Weber³, Silke Böttcher⁴, Uta Sekanina⁵, Thomas Asendorf⁶, Eva Hummers⁵, Michael Freitag⁴, Nils Schneider³, Tim Friede⁶, Friedemann Nauck⁷, Martin Scherer², Gabriella Marx^{2#}, Judith Dams^{1#}

¹Department of Health Economics and Health Services Research, University Medical Center Hamburg-Eppendorf, Hamburg Center for Health Economics, Hamburg, Germany; ²Department of General Practice and Primary Care, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; ³Institute for General Practice and Palliative Care, Hannover Medical School, Hannover, Germany; ⁴Division of General Practice, Carl von Ossietzky University of Oldenburg, Oldenburg, Germany; ⁵Department of General Practice, University Medical Center Goettingen, Goettingen, Germany; ⁶Department of Medical Statistics, University Medical Center Goettingen, Goettingen, Germany; ⁷Department of Palliative Medicine, University Medical Center Goettingen, Goettingen, Germany

Contributions: (I) Conception and design: G Marx, T Mallon, E Hummers, M Freitag, N Schneider, T Friede, F Nauck, M Scherer, J Dams, HH König, S Gottschalk; (II) Administrative support: None; (III) Provision of study materials or patients: T Friede, T Asendorf; (IV) Collection and assembly of data: T Mallon, J Schulze, J Weber, S Böttcher, U Sekanina; (V) Data analysis and interpretation: S Gottschalk, J Dams, HH König; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Sophie Gottschalk, PhD. Department of Health Economics and Health Services Research, University Medical Center Hamburg-Eppendorf, Hamburg Center for Health Economics, Martinistraße 52, 20246 Hamburg, Germany. Email: s.gottschalk@uke.de.

Background: Worldwide, progressive chronic, non-malignant diseases are highly prevalent. Especially with increasing age, they are characterised by high hospitalisation rates and high healthcare costs. Improved interprofessional collaboration between general practitioners (GPs) and specialist palliative home care (SPHC) teams might reduce hospitalisation while improving symptoms and quality of life, or preventing them from deterioration. The aim of this study was to examine the cost-effectiveness of a newly developed intervention in patients with advanced chronic, non-malignant diseases consisting of a structured palliative care nurse-patient consultation followed by an interprofessional telephone case conference.

Methods: The analysis was based on data from 172 participants of the KOPAL multi-centre, cluster randomised controlled trial. Patients with advanced congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), or dementia were randomised into intervention group (IG) and control group (CG, usual care). Cost-effectiveness was examined over 48 weeks from a societal and healthcare payer's perspective. Effects were quantified as quality-adjusted life years (QALYs, EQ-5D-5L). Incremental cost-effectiveness ratios were calculated and cost-effectiveness acceptability curves were constructed.

Results: Baseline imbalances in costs and effects could be observed between IG and CG. After adjusting for these imbalances and compared to the CG, mean costs in the IG were non-significantly higher from a societal and lower from a payer's perspective. On the effect side, the IG had marginally lower mean QALYs. The results were characterized by high statistical uncertainty, indicated by large confidence intervals for the cost and effect differences between groups and probabilities of cost-effectiveness between 18% and 65%, depending on the perspective and willingness-to-pay.

✳ Special series on Value of Palliative Care.

[^] ORCID: 0000-0002-6912-6256.

Conclusions: Based on the results of this study, the cost-effectiveness of the KOPAL intervention was uncertain. The results highlighted (methodological) challenges of economic evaluations in patients with chronic, non-malignant diseases related to sample size, heterogeneity of participants, and the way the intervention effectiveness is typically captured in economic evaluations.

Keywords: Economic evaluation; cost-effectiveness; costs; palliative care

Submitted Jan 25, 2023. Accepted for publication Aug 30, 2023. Published online Oct 18, 2023.

doi: 10.21037/apm-23-88

View this article at: <https://dx.doi.org/10.21037/apm-23-88>

Introduction

Worldwide, chronic non-malignant diseases (CNMD) like chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF) and dementia are on the rise and are among the top ten contributors to the burden of disease in older people (1). The disease trajectory is characterized by a continuous decline of functional status with phases of acute exacerbation, often requiring hospitalisation (2). These hospitalisations substantially contribute to the high economic burden of CNMD (2-4). Apart from hospitalisations, palliative care needs of patients with CNMD in Germany are mainly managed in the outpatient setting by general practitioners (GPs) (5), who can prescribe

professional specialist palliative home care (SPHC) to maintain quality of life and enable patients to live in their familiar surroundings until death. Studies have shown that (specialist) palliative home care can improve quality of care and save healthcare costs (6,7). However, there seem to be barriers to successful collaboration between GPs and SPHC teams (consisting of specialist palliative care physicians and nurses), such as a lack of information flow (8,9). Therefore, improving interprofessional collaboration and exchange between GPs and SPHC teams seems crucial for improving palliative care (10). In an Australian pilot study, a single interdisciplinary case conference between the GP and palliative care specialists led to a reduction of emergency department and general hospital admissions and hospitalisation costs (11,12). Based on this promising example, an intervention consisting of a structured SPHC nurse-patient consultation followed by an interprofessional telephone case conference was developed in the KOPAL project, with the primary aim of reducing hospitalisations in patients with CNMD through enhanced collaboration between GPs and SPHC teams (13). This reduction in the number of hospitalisations is desirable from an economic perspective, especially in light of the projected increase in demand for palliative care and the associated need to make allocative decisions against the backdrop of scarce resources. Economic evaluations aim to inform these decisions by examining the relationship between costs and effects of interventions. However, in the context of palliative care, economic evaluations are sparse because interventions are often complex and not standardised, and outcomes vary, e.g., depending on the number and combination of comorbidities (14-17). Most health economic research in palliative care has focused only on cost savings, with predominantly positive results (18,19). However, these studies often fail to capture the full economic costs of palliative care, but focus on certain cost types (e.g., hospitalisations) and therefore neglect cost categories outside the healthcare

Highlight box

Key findings

- Cost-effectiveness of the KOPAL intervention in patients with advanced chronic non-malignant diseases (CNMD) is uncertain.

What is known and what is new?

- Improved interprofessional collaboration between general practitioners and specialist palliative home care teams might reduce hospitalisation while improving symptoms and quality of life of patients with CNMD.
- The current study presents the within-trial cost-effectiveness analysis of the KOPAL intervention, a structured palliative care nurse-patient consultation followed by an interprofessional telephone case conference. Depending on the perspective and willingness-to-pay per quality-adjusted life year, the probability of cost-effectiveness was between 18% and 65%.

What is the implication, and what should change now?

- The results were characterised by high statistical uncertainty and should therefore be interpreted with caution. The high uncertainty can be attributed to the small sample size, high heterogeneity and influential outliers, which exemplifies challenges of economic evaluations in the palliative care context to be considered in designing future studies.

system (e.g., costs of informal care) (16,18). These cost categories in particular account for a large share of the full costs of palliative care and are highly relevant from a societal perspective (20,21). Therefore, a comprehensive societal perspective should be adopted which enables to observe cost-shifting between sectors (e.g., from inpatient to outpatient sector or to informal carers) (22). Moreover, as palliative care is not only about costs, but mainly about the value of care, it seems crucial to move from pure cost analyses to evaluations of efficiency of palliative care, meaning to focus on value for money or the relationship between costs and effects (22,23).

Objective

The aim of this study was to examine the cost-effectiveness of a structured SPHC nurse-patient consultation followed by an interprofessional telephone case conference (the KOPAL intervention) in patients with advanced CNMD from a societal and healthcare payer perspective. We present this article in accordance with the CHEERS reporting checklist (24) (available at <https://apm.amegroups.com/article/view/10.21037/apm-23-88/rc>).

Methods

The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the local ethics committee of the Medical Association Hamburg, Germany (No. PV7090) as well as the ethics committees of the University Medical Centre Goettingen, Germany (No. 34/1/20Ü), the Hannover Medical School (No. 8815 BO K 2019) and the University of Oldenburg (No. 2019–145) and informed consent was taken from all individual participants. The trial is registered on the German clinical trial register (registration No. DRKS00017795; 17 November 2021, V.05).

Study design and sample

The analysis was based on data from the multicentre, two-arm, cluster randomised controlled trial KOPAL. In KOPAL, SPHC teams with a specialised palliative care qualification were invited from 2 regions in Northern Germany: Hamburg (study centre Hamburg) and Lower Saxony (study centres Göttingen, Oldenburg, and Hanover). Subsequently, GPs in the respective regions were invited to screen their patients for eligibility based

on the following criteria: late-stage CHF [New York Heart Association (NYHA) classification 3–4 and at least one hospital admission in the last 12 months], COPD [Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage classification 3–4, group D, and Modified Medical Research Council (mMRC) grade 2 or higher], or dementia [Global Deterioration Scale (GDS) grade 4 or higher], and at least one GP consultation in the past 3 months. Patients with a cancer diagnosis in the last 5 years or currently receiving SPHC support were not eligible. Eligible patients were invited to the study by the GPs in written form. Interested patients could send a contact form to the study centres, which arranged a personal or telephone meeting to provide more detailed information of the study and obtain informed consent for participation in the study. After providing informed consent, participants were block-randomised on practice level into intervention group (IG) and control group (CG, usual care). For people with dementia and other participants unable to give informed consent, a legal representative (family member) signed the consent form on behalf of the participant and acted as a proxy in answering the questionnaires at the assessments. Data collection took place at baseline (T0) and after 6 (T1), 12 (T2), 24 (T3), and 48 weeks (T4) post baseline. Detailed information on the study design can be found in the study protocol (13).

Interventions and intervention costs

The KOPAL intervention consisted of (I) a SPHC nurse-patient consultation to assess the participant's current life and health situation; (II) a brief consultation between the SPHC nurse and the SPHC physician; and (III) an interprofessional telephone case conference between the SPHC nurse, the SPHC physician, and the GP (13). Intervention costs were calculated by valuing the average duration of the intervention components with average labour costs of the respective professionals, resulting in intervention costs per participant of €174 (Table S1).

Health service use and costs

Health services use in the areas outpatient care (physician and non-physician), formal care/support (day care, respite care, ambulatory care, payed household help), informal care/support, medical aids, and medication was assessed at each assessment time point using an adapted version of the questionnaire for the use of medical and non-medical

services in old age (FIMA) (25) (6 [T1, T2], 12 [T0, T3], or 24 weeks [T4] retrospectively). Information on inpatient services use (general/psychiatric hospitalisation and rehabilitation) was collected from the GP at T0 and T4 (48 weeks retrospectively). Resource use was monetarily valued using standardised unit costs for Germany (26), inflated to the year 2020 (27), and pharmacy retail prices (28). Costs were reported in 2020 euros (€) and were not discounted as the time horizon was 48 weeks (≤ 12 months). Productivity loss was not considered as the majority of participants was above working age or had already been receiving disability pension before participating in the study.

Effects

For the current cost-effectiveness analysis, effects were quantified as quality-adjusted life years (QALYs) based on the EQ-5D-5L health-related quality of life questionnaire (29,30). The EQ-5D-5L consists of the dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each being rated by the participants on a scale ranging from 'no problems' (1) to 'extreme problems' (5). These answers were transformed to an index, with 1 representing 'perfect health' (no problems in all dimension) and 0 representing 'death', by applying general population weights to each severity level in the 5 dimensions (31). Negative index values are possible and represent health states 'worse than death'. QALYs were obtained as weighted linear combinations of the EQ-5D indices from the four follow-up assessment time points (compare Figure S1). For participants who died within the observation period, the EQ-5D index was set to zero for subsequent time points, and the time until death was accounted for in the calculation of QALYs.

Statistical analysis

The current analysis was detailed in the proposal of the KOPAL trial. Beyond that, no separate health economic analysis plan was published. The cost-effectiveness analysis was conducted based on the intention-to-treat principle, including all randomised participants with at least a baseline assessment ($n=172$). Of these, missing data due to drop-out, missing individual assessments, or missing information in individual items of the EQ-5D or resource use were imputed. The proportion of missing values across the variables of interest for the cost-effectiveness analysis did not exceed 27%. Overall, data was complete for

72% of the sample. Fifty imputed datasets were created using multiple imputation by chained equation (MICE) with predictive mean matching as imputation method (32,33). Estimations were performed separately in each imputed dataset and combined using Rubin's rule (34).

Unadjusted mean costs and effects in the year prior to baseline and after 48 weeks follow-up were calculated for the IG and CG. Additionally, for data after 48 weeks follow-up, differences in mean total costs from a societal perspective (including informal care costs) and payer's perspective (excluding informal care costs) between IG and CG were calculated using mixed-effects generalised linear models with a gamma distribution and log-link function adjusted for the following baseline characteristics: gender, age, health insurance status (statutory or privately insured), number of comorbidities, total costs, EQ-5D index (fixed effects) and the GP practices (random effect). The mean between-group difference in QALYs over 48 weeks was calculated using a linear mixed-effects model and adjusting for the same covariates.

Cost-effectiveness of the KOPAL intervention compared to the CG was examined by calculating the incremental cost-effectiveness ratio (ICER) as the difference in mean costs divided by the difference in mean effects ($ICER = \Delta C / \Delta E$). Moreover, cost-effectiveness was examined using the net-benefit approach to determine the probability of cost-effectiveness depending on the willingness to pay (WTP) for an additional QALY (35-37). For this purpose, the individual net monetary benefit (NMB_i) was calculated as $NMB_i = \lambda \cdot E_i - C_i$, with λ representing the willingness to pay, E_i the individual effect (QALYs), and C_i representing the individual costs from a societal or payer's perspective, respectively. The NMB_i was then used as dependent variable in a linear mixed-effects model including the group variable as well as baseline gender, age, health insurance status, number of comorbidities, total costs, and EQ-5D index as fixed effects and the GP practices as random effect. The analyses were rerun assuming different WTP levels between €0 and €120,000. The probabilities of cost-effectiveness at certain WTP levels were derived from the P value of the coefficient δ of the group variable ($1-P/2$ if $\delta > 0$; $P/2$ if $\delta < 0$) and presented as cost-effectiveness acceptability curves (CEAC) (38).

In a sensitivity analysis, two outliers in the CG with high utilisation of formal care were excluded from the analyses to examine the influence of these outliers on the cost-effectiveness results.

All analyses were conducted using STATA/MP 17.0 (StataCorp. 2021. Stata Statistical Software: Release 17.

Table 1 Sample characteristics

| Characteristics | Intervention (n=84) | Control (n=88) |
|---|---------------------|-------------------|
| Age, years, mean (SE) | 75.46 (1.07) | 77.01 (1.05) |
| Female, n (%) | 35 (41.67) | 43 (48.86) |
| Body mass index [†] , kg/m ² , mean (SE) | 26.95 (0.68) | 27.05 (0.76) |
| Income [†] , €, mean (SE) | 1,645.24 (97.03) | 1,678.67 (100.37) |
| Number of comorbidities [‡] , mean (SE) | 3.98 (0.23) | 3.88 (0.21) |
| CHF, n (%) | 39 (46.43) | 42 (47.73) |
| COPD, n (%) | 33 (39.29) | 35 (39.77) |
| Dementia, n (%) | 20 (23.81) | 20 (22.73) |
| Proxy interview, n (%) | 27 (32.14) | 23 (26.14) |
| Subjective health (EQ-VAS), mean (SE) | 48.81 (2.12) | 48.05 (2.24) |
| Number of children [†] , mean (SE) | 1.58 (0.15) | 1.82 (0.16) |
| Statutory insured, n (%) | 82 (97.62) | 69 (78.41) |
| Independently living, n (%) | 81 (96.43) | 85 (96.59) |
| Marital status, n (%) | | |
| Never married | 5 (5.95) | 10 (11.36) |
| Married | 47 (55.95) | 50 (56.82) |
| Divorced | 10 (11.90) | 5 (5.68) |
| Widowed | 22 (26.19) | 23 (26.14) |
| Education, n (%) | | |
| Secondary/primary school graduate | 55 (65.48) | 55 (62.50) |
| Middle school/junior high/polytechnic graduate | 17 (20.24) | 15 (17.05) |
| Technical college graduate | 6 (7.14) | 4 (4.55) |
| High school diploma/extended high school | 5 (5.95) | 12 (13.64) |
| No certificate | 1 (1.19) | 2 (2.27) |
| Number of deaths (between baseline and 48 weeks follow-up), n (%) | 11 (13.10) | 9 (10.23) |

[†], missing values were imputed; [‡], CHF & COPD are included in number of comorbidities. SE, standard error; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; EQ-VAS, EQ-visual analogue scale.

College Station, TX: StataCorp LLC). The two-sided significance level was set to 0.05.

Results

In *Table 1*, sample characteristics are displayed for IG (n=84) and CG (n=88) separately. Groups were balanced for the majority of variables, but individuals in the IG were slightly younger (mean age 75.5 *vs.* 77.0 years), less likely to be female (42% *vs.* 49%), and the interviews were more often

conducted with proxies (32% *vs.* 26%).

Imbalances between IG and CG at baseline were also observed at cost level, with the IG having lower mean inpatient (−€2,305, 95% CI: −8,507 to 3,897) and formal care costs (−€1,443, 95% CI: −3,857 to 971) and higher informal care costs (€31,853, 95% CI: 11,936 to 51,769) in the year prior to enrolment (*Table 2*). Moreover, health-related quality of life (mean EQ-5D index) was lower in the IG than in the CG (−0.12, 95% CI: −0.21 to −0.03).

After 48 weeks follow-up, 11 participants (13%) in the

Table 2 Costs (in 2020 euros) and health-related quality of life (EQ-5D index) at baseline

| Category | Intervention (n=84) | Control (n=88) | Difference |
|-------------------------------|---------------------------|---------------------------|---------------------------|
| Inpatient services | 8,736 (5,635 to 11,837) | 11,041 (5,754 to 16,328) | -2,305 (-8,507 to 3,897) |
| General hospital | 8,350 (5,375 to 11,325) | 10,514 (5,335 to 15,693) | -2,164 (-8,210 to 3,882) |
| Psychiatry | 5 (-14 to 23) | 291 (-205 to 787) | -286 (-794 to 222) |
| Rehabilitation | 381 (160 to 602) | 236 (36 to 436) | 145 (-152 to 443) |
| Outpatient services | 3,018 (1,488 to 4,549) | 2,719 (1,898 to 3,541) | 299 (-1,417 to 2,014) |
| Physician | 2,398 (884 to 3,912) | 2,117 (1,309 to 2,925) | 282 (-1,413 to 1,976) |
| Therapist | 620 (389 to 850) | 603 (361 to 844) | 17 (-318 to 352) |
| Formal support | 2,487 (1,493 to 3,480) | 3,930 (1,771 to 6,089) | -1,443 (-3,857 to 971) |
| Informal support | 51,391 (33,263 to 69,518) | 19,538 (10,640 to 28,436) | 31,853 (11,936 to 51,769) |
| Medical aids | 556 (169 to 942) | 825 (65 to 1,586) | -270 (-1,136 to 596) |
| Medications | 2,233 (1,755 to 2,711) | 1,889 (1,590 to 2,188) | 344 (-214 to 902) |
| Total costs (SP) | 68,420 (49,660 to 87,180) | 39,942 (27,889 to 51,996) | 28,478 (6,379 to 50,576) |
| Total costs (PP) [†] | 17,029 (13,402 to 20,656) | 20,404 (14,469 to 26,340) | -3,375 (-10,411 to 3,661) |
| EQ-5D index | 0.56 (0.48 to 0.63) | 0.68 (0.63 to 0.73) | -0.12 (-0.21 to -0.03) |

Data are presented as mean (95% CI). [†], excluding informal care costs. CI, confidence interval; SP, societal perspective; PP, payer's perspective.

IG and 9 participants (10%) in the CG had died. The differences in formal and informal care costs between IG and CG observed at baseline remained, resulting in higher unadjusted total costs from the societal perspective (€25,836, 95% CI: 2,721 to 48,952) and lower total costs from the healthcare payer perspective (-€1,685, 95% CI: -8,952 to 5,582) (Table 3; unadjusted mean costs and QALYs after 24 weeks are reported in Table S2). Adjusted for baseline differences, the difference in total costs from the societal perspective was mitigated, but the estimate still pointed towards higher costs in the IG (€9,560, 95% CI: -17,871 to 36,991). Similarly, the QALY difference decreased from -0.08 (95% CI: -0.16 to 0.002) in the unadjusted analysis to -0.01 (95% CI: -0.07 to 0.04) in the adjusted analysis.

Based on the unadjusted cost and effect differences, the ICER point estimate indicated dominance of the CG (IG was more costly and less effective) from the societal perspective. From the payer's perspective, the ICER indicated cost-saving for the IG, but at lower effectiveness. Assuming hypothetical WTP values between €0 and €120,000, the CEAC based on the adjusted net-benefit regressions showed probabilities of the KOPAL intervention being cost-effective between 20% and 18% from a societal perspective, and between 65% and 33%

from a payer's perspective (Figure 1). Excluding outliers with high informal care utilisation had a huge influence on the CEAC from the payer's perspective, resulting in a more than 10% reduced probability of KOPAL being cost-effective compared to usual care (Figure 1).

Discussion

Key findings

The current study examined the cost-effectiveness of a SPHC nurse-patient consultation followed by an interprofessional telephone case conference among patients with non-oncological palliative care needs. The results pointed towards higher costs for the IG compared to the CG from a societal perspective (driven by higher informal care costs) and lower costs for the IG from a payer's perspective, but these did not reach statistical significance. On the effect side, the QALY point estimate was marginally and non-significantly lower in the IG. Overall, the results were characterized by high statistical uncertainty, indicated by large confidence intervals for the cost and effect differences between groups and probabilities of cost-effectiveness in the CEACs between 18% and 65%, depending on the perspective and WTP.

Table 3 Costs (in 2020 euros) and effects at 48 weeks

| Category | Intervention (n=84) | Control (n=88) | Difference |
|-------------------------------|----------------------------|---------------------------|---------------------------|
| Inpatient services | 9,666 (4,788 to 14,544) | 9,432 (5,611 to 13,254) | 234 (–5,910 to 6,378) |
| General hospital | 8,944 (4,098 to 13,790) | 9,356 (5,573 to 13,139) | –412 (–6,506 to 5,682) |
| Psychiatry | 520 (–66 to 1,106) | 0 (0 to 0) | 520 (–52 to 1,092) |
| Rehabilitation | 202 (–9 to 414) | 77 (–35 to 188) | 126 (–103 to 355) |
| Outpatient services | 2,175 (1,538 to 2,812) | 2,208 (1,413 to 3,002) | –33 (–1,058 to 992) |
| Physician | 1,554 (959 to 2,148) | 1,551 (817 to 2,285) | 3 (–948 to 953) |
| Therapist | 621 (442 to 800) | 657 (387 to 926) | –35 (–361 to 290) |
| Formal support | 2,646 (1,577 to 3,716) | 4,609 (1,984 to 7,234) | –1,963 (–4,844 to 919) |
| Informal support | 55,721 (37,888 to 73,554) | 28,200 (16,156 to 40,244) | 27,521 (6,195 to 48,848) |
| Medical aids | 331 (134 to 529) | 549 (257 to 842) | –218 (–571 to 135) |
| Medications | 2,224 (1,788 to 2,660) | 2,103 (1,757 to 2,450) | 121 (–436 to 677) |
| Intervention | 174 | 0 | 174 |
| Total costs (SP) | 72,938 (53,750 to 92,126) | 47,101 (33,956 to 60,247) | 25,836 (2,721 to 48,952) |
| Adjusted [†] | 78,100 (51,118 to 105,082) | 68,541 (42,940 to 94,141) | 9,560 (–17,871 to 36,991) |
| Total costs (PP) [‡] | 17,217 (11,954 to 22,480) | 18,902 (13,862 to 23,941) | –1,685 (–8,952 to 5,582) |
| Adjusted [†] | 17,908 (13,149 to 22,667) | 19,636 (14,577 to 24,695) | –1,728 (–8,390 to 4,934) |
| Effects (QALY) | 0.52 (0.46 to 0.58) | 0.6 (0.54 to 0.65) | –0.08 (–0.16 to 0.002) |
| Adjusted [†] | 0.55 (0.51 to 0.59) | 0.56 (0.53 to 0.60) | –0.01 (–0.07 to 0.04) |

Data are presented as mean (95% CI). [†], based on mixed-effects (generalised) linear models adjusted for the following baseline characteristics: gender, age, health insurance status (statutory or privately insured), number of comorbidities, total costs, EQ-5D index (fixed effects) and the GP practices (random effect); [‡], excluding informal care costs. SP, societal perspective; PP, payer's perspective; QALY, quality-adjusted life year; CI, confidence interval; GP, general practitioner.

During the analyses, several challenges were encountered that may also apply to a broader context of economic evaluations in persons at the end of life or with palliative care needs.

Sample size and heterogeneity of participants

The cost-effectiveness analysis in this study was faced with a small and heterogeneous sample, resulting in individual cases having a high influence on the overall results, as shown in the sensitivity analysis. The onset of the COVID-19 pandemic in March 2020 and the resulting contact restrictions and increased workload of GPs, who functioned as gatekeepers for the recruitment of eligible participants, challenged recruitment to the KOPAL study. This resulted in a considerably smaller sample size (n=172) than initially planned (n=616) (13). Similar to trial-based economic evaluations outside the palliative setting, such small sample sizes lead to insufficient power caused

by skewed costs and effects (39). This is especially true for patients with advanced chronic conditions, who are heterogeneous and complex in terms of disease course and number/type of comorbidities, which in turn leads to large variances and uncertainty in costs and effects across individuals and diseases. This was also evident in data from the KOPAL study, where participants with COPD and CHF had rather high hospitalisation cost, whereas informal care costs were highest for people with dementia. Moreover, outliers (e.g., individual patients with extremely high costs or effects) had a high influence on the estimated mean costs, effects, or ICER. Small sample sizes increase the risk of such influential patients being randomly assigned to either the IG or CG, thus biasing the estimates in one direction or the other. However, simply excluding these outliers from the analyses does not seem justified either, as such patients also exist in reality and may be those to be addressed by the intervention. Excluding such cases would potentially

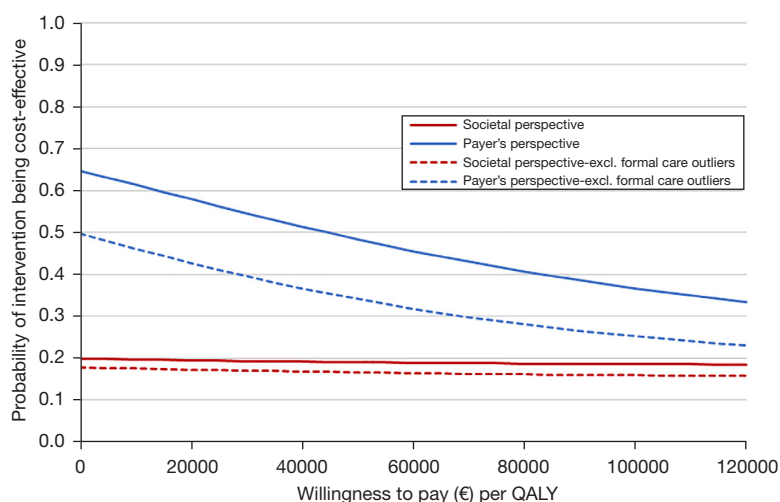


Figure 1 Cost-effectiveness acceptability curves from a societal and payer's cost perspective. Probability of the KOPAL intervention being cost-effective at different willingness to pay values per QALY gained. The dashed lines represent the results of sensitivity analyses excluding two outliers in the control group with high utilisation of formal care. QALY, quality-adjusted life year.

underestimate the costs of palliative care. Thus, specifically in the palliative care context, adequate sample sizes are key to better understand or account for the complexity of palliative care in economic evaluations (19).

Capturing effectiveness

In general, it is acknowledged by experts from the palliative care field that the aim of economic evaluations, that is to inform allocative decision-making, requires generic outcomes such as the QALY (40). For measuring the quality component of a QALY, generic instruments of health-related quality of life, such as the EQ-5D, have prevailed and were therefore also used in this study. Based on the results, the KOPAL intervention did not seem to have an effect on patients' health-related quality of life as measured by the EQ-5D-5L. Similarly, a study from Australia found no improvement in participants' global quality of life following a case conference (41). This may be explained by the fact that the KOPAL intervention is a rather low-threshold concept to strengthen the interprofessional collaboration among GPs and SPHC teams, which also means that there is no standardised intervention that each participant in the IG received. Instead, it was kept flexible to which extent changes in treatment strategies were initiated following the structured SPHC nurse-patient consultation and the interprofessional case conference. This flexibility ensures to pay more attention to the needs of individual patients, but could have led to heterogeneous treatment effects on the

patient level (e.g., on health-related quality of life).

Beyond that, it could be argued that the EQ-5D is not suitable for capturing effectiveness of interventions in persons with palliative care needs, as its dimensions are function-oriented and do insufficiently represent dimensions that are important for persons at the end of life (40,42). Moreover, the use of general population preferences for valuing restrictions in the individual dimensions can be questioned, as these may differ from the preferences of the affected person(s) (43). These issues can be addressed by future studies in several directions, e.g., by letting persons at the end-of-life value their health and/or by using instruments that better capture relevant dimensions of health or well-being at the end of life (42,43).

In addition, it is possible that interventions aimed at improving care management do not, or not primarily, affect the patients' health-related quality of life, but rather the patient's surrounding environment (e.g., informal carers). Informal care costs among persons receiving end-of-life or palliative care are substantial and account for a high proportion of total costs (20). From a societal perspective, it would therefore be relevant to incorporate potential benefits of palliative care interventions for informal carers into the cost-effectiveness framework. Possible options include either measuring care-related quality of life with available preference-based instruments [e.g., ASCOT-Carer (44) or CarerQoL (45)] or using the new EQ Health and Wellbeing (EQ-HWB) instrument (46), which was

specifically designed to capture impacts of interventions across health and social care settings (including carers), thereby allowing for comparisons of effectiveness, e.g., between patients and carers.

While these directions remain relevant for future studies, it is unclear whether or how the use of an alternative instrument in this specific study would have changed the results, as no statistically significant differences between IG and CG were found in other quantitative endpoints of this study either (e.g., pain or symptom burden) (unpublished data). However, as discussed previously, this could also be related to the low power due to the small size and the heterogeneity of the sample.

Limitations

Some limitations specific to this study should also be mentioned. First, the monetisation of hospital stays only distinguished between days in intensive care and all other days in hospital. No further differentiation (e.g., between days on palliative care ward and “normal ward”) was made, as no standardised unit costs were available for this. Second, a proxy reporting bias cannot be ruled out, as for participants with dementia (and occasionally also for participants with CHF/COPD) the interviews were conducted with a relative. There is evidence in the literature that self-reported quality of life differs from quality of life assessed by proxies, with proxies usually reporting lower levels of quality of life (47). Similarly, there may have been differences between proxy- and self-reported informal care time. Third, informal care was valued in this study using the opportunity cost approach, in which informal care hours were valued by average labour costs per hour. Using other approaches to value informal care (e.g., assuming the costs needed to replace informal care with formal care) would have resulted in different total amounts of informal care costs, but the direction of the between-group difference would have remained.

Conclusions

Based on the results of this study, the cost-effectiveness of the KOPAL intervention was uncertain with probabilities of cost-effectiveness between 18% and 65%, depending on the perspective and WTP. The results exemplify challenges of economic evaluations in the palliative or end-of-life context, especially with regard to sample size and heterogeneity, as well as measuring effectiveness, which should be considered in the design of future studies.

Acknowledgments

KOPAL is a multicentre cluster randomised controlled trial that was made possible by good interdisciplinary cooperation. The applicants are Prof. Martin Scherer (study director), Dr. Gabriella Marx (co-study director), Dr. Ingmar Schäfer, Prof. Hendrik van den Bussche, Prof. Nils Schneider, PD Stephanie Stiel, Prof. Eva Hummers, Prof. Michael Freitag, Prof. Friedemann Nauck, Prof. Tim Friede, Prof. Hans-Helmut König. We would like to thank the scientific advisory board as well as all patients, relatives, general practitioners and specialist palliative care teams who participated in the KOPAL study and supported the study with their data and commitment.

Funding: This work was supported by the Federal Joint Committee (G-BA, No. 01VSF18024, funding period: 06/2019 – 05/2022). The funding source takes no part in the collection, analysis and interpretation of data, in the writing of the manuscript or in the decision to submit the manuscript for publication.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Claudia Fischer) for the series “Value of Palliative Care” published in *Annals of Palliative Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at <https://apm.amegroups.com/article/view/10.21037/apm-23-88/rc>

Data Sharing Statement: Available at <https://apm.amegroups.com/article/view/10.21037/apm-23-88/dss>

Peer Review File: Available at <https://apm.amegroups.com/article/view/10.21037/apm-23-88/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroups.com/article/view/10.21037/apm-23-88/coif>). The series “Value of Palliative Care” was commissioned by the editorial office without any funding or sponsorship. T.F. reports personal fees from Aslan, Bayer, BiosenseWebster, Bristol Myers Squibb, CSL Behring, Enanta, Fresenius Kabi, Galapagos, Immunic, IQVIA, Janssen, Johnson & Johnson Medical, KyowaKirin, LivaNova, Minoryx, Novartis, RECARDIO, Recordati, Relaxera, Roche,

Servier, Viatrix, VICO Therapeutics and Vifor for statistical consultancies including data monitoring committees, all outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the local ethics committee of the Medical Association Hamburg, Germany (No. PV7090) as well as the ethics committees of the University Medical Centre Goettingen, Germany (No. 34/1/20Ü), the Hannover Medical School (No. 8815 BO K 2019) and the University of Oldenburg (No. 2019–145) and informed consent was taken from all individual participants. The trial is registered on the German clinical trial register (registration No. DRKS00017795; 17 November 2021, V.05).

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Prince MJ, Wu F, Guo Y, et al. The burden of disease in older people and implications for health policy and practice. *Lancet* 2015;385:549-62.
2. Hollingworth W, Biswas M, Maishman RL, et al. The healthcare costs of heart failure during the last five years of life: A retrospective cohort study. *Int J Cardiol* 2016;224:132-8.
3. Iheanacho I, Zhang S, King D, et al. Economic Burden of Chronic Obstructive Pulmonary Disease (COPD): A Systematic Literature Review. *Int J Chron Obstruct Pulmon Dis* 2020;15:439-60.
4. Giles L, Freeman C, Field P, et al. Humanistic burden and economic impact of heart failure? A systematic review of the literature. *F1000Research* 2020;8:859.
5. Becka D, Riese A, Rychlik RP, et al. General practitioners in palliative care in Germany: a systematic review. *Dtsch Med Wochenschr* 2014;139:2254-8.
6. Maetens A, Beernaert K, De Schreye R, et al. Impact of palliative home care support on the quality and costs of care at the end of life: a population-level matched cohort study. *BMJ Open* 2019;9:e025180.
7. Gonzalez-Jaramillo V, Fuhrer V, Gonzalez-Jaramillo N, et al. Impact of home-based palliative care on health care costs and hospital use: A systematic review. *Palliat Support Care* 2021;19:474-87.
8. Schneider N, Engeser P, Behmann M, et al. Specialized outpatient palliative care. The expectations of general practitioners. *Schmerz* 2011;25:166, 168-173. Erratum in: *Schmerz* 2011;25:336-8.
9. Kaiser F, Sohm M, Illig D, et al. Four years of specialized outpatient palliative care in a rural area: Cooperation and acceptability from general practitioners' view. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2016;59:916-20.
10. Behmann M, Jünger S, Radbruch L, et al. Public health actions to improve palliative care in Germany: results of a three-round Delphi study. *Health Policy* 2012;106:303-12.
11. Mitchell G, Zhang J, Burridge L, et al. Case conferences between general practitioners and specialist teams to plan end of life care of people with end stage heart failure and lung disease: an exploratory pilot study. *BMC Palliat Care* 2014;13:24.
12. Hollingworth S, Zhang J, Vaikuntam BP, et al. Case conference primary-secondary care planning at end of life can reduce the cost of hospitalisations. *BMC Palliat Care* 2016;15:84.
13. Marx G, Mallon T, Pohontsch NJ, et al. Effectiveness of a specialist palliative home care nurse-patient consultation followed by an interprofessional telephone case conference compared with usual care among patients with non-oncological palliative care needs: protocol for the multicentre KOPAL cluster-randomised controlled trial. *BMJ Open* 2022;12:e059440.
14. Davis MA, Nallamotheu BK, Banerjee M, et al. Identification Of Four Unique Spending Patterns Among Older Adults In The Last Year Of Life Challenges Standard Assumptions. *Health Aff (Millwood)* 2016;35:1316-23.
15. May P, Garrido MM, Cassel JB, et al. Palliative Care Teams' Cost-Saving Effect Is Larger For Cancer Patients With Higher Numbers Of Comorbidities. *Health Aff (Millwood)* 2016;35:44-53.
16. Gardiner C, Ingleton C, Ryan T, et al. What cost

- components are relevant for economic evaluations of palliative care, and what approaches are used to measure these costs? A systematic review. *Palliat Med* 2017;31:323-37.
17. Normand C. Setting priorities in and for end-of-life care: challenges in the application of economic evaluation. *Health Econ Policy Law* 2012;7:431-9.
 18. Smith S, Brick A, O'Hara S, et al. Evidence on the cost and cost-effectiveness of palliative care: a literature review. *Palliat Med* 2014;28:130-50.
 19. Mathew C, Hsu AT, Prentice M, et al. Economic evaluations of palliative care models: A systematic review. *Palliat Med* 2020;34:69-82.
 20. Gardiner C, Breerton L, Frey R, et al. Exploring the financial impact of caring for family members receiving palliative and end-of-life care: a systematic review of the literature. *Palliat Med* 2014;28:375-90.
 21. Gardiner C, Robinson J, Connolly M, et al. Equity and the financial costs of informal caregiving in palliative care: a critical debate. *BMC Palliat Care* 2020;19:71.
 22. May P, Cassel JB. Economic outcomes in palliative and end-of-life care: current state of affairs. *Ann Palliat Med* 2018;7:S244-8.
 23. McCaffrey N, Cassel JB, Coast J. An economic view on the current state of the economics of palliative and end-of-life care. *Palliat Med* 2017;31:291-2.
 24. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. *Value Health* 2022;25:3-9.
 25. Seidl H, Bowles D, Bock JO, et al. FIMA--questionnaire for health-related resource use in an elderly population: development and pilot study. *Gesundheitswesen* 2015;77:46-52.
 26. Bock JO, Brettschneider C, Seidl H, et al. Calculation of standardised unit costs from a societal perspective for health economic evaluation. *Gesundheitswesen* 2015;77:53-61.
 27. Inflation (CPI) (indicator) [database on the Internet]. OECD. 2022. doi: 10.1787/eee82e6e-en. Accessed: 21 November 2022
 28. Rote Liste Service GmbH. ROTE LISTE 2020: Pharmaceutical directory for Germany (including EU approvals and certain medical devices). Frankfurt/Main: Rote Liste Service GmbH; 2020.
 29. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.
 30. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727-36.
 31. Ludwig K, Graf von der Schulenburg JM, Greiner W. German Value Set for the EQ-5D-5L. *Pharmacoeconomics* 2018;36:663-74.
 32. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30:377-99.
 33. StatCorp. Stata multiple-imputation reference manual. Release 16. College Station, TX: StataCorp LLC; 2019.
 34. Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987.
 35. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998;18:S68-80.
 36. Zethraeus N, Johannesson M, Jönsson B, et al. Advantages of using the net-benefit approach for analysing uncertainty in economic evaluation studies. *Pharmacoeconomics* 2003;21:39-48.
 37. Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. *Health Econ* 2002;11:415-30.
 38. Hoch JS, Rockx MA, Krahn AD. Using the net benefit regression framework to construct cost-effectiveness acceptability curves: an example using data from a trial of external loop recorders versus Holter monitoring for ambulatory monitoring of "community acquired" syncope. *BMC Health Serv Res* 2006;6:68.
 39. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II--An ISPOR Good Research Practices Task Force report. *Value Health* 2015;18:161-72.
 40. Wichmann AB, Goltstein LCMJ, Obihara NJ, et al. QALY-time: experts' view on the use of the quality-adjusted LIFE year in COST-effectiveness analysis in palliative care. *BMC Health Serv Res* 2020;20:659.
 41. Mitchell GK, Del Mar CB, O'Rourke PK, et al. Do case conferences between general practitioners and specialist palliative care services improve quality of life? A randomised controlled trial (ISRCTN 52269003). *Palliat Med* 2008;22:904-12.
 42. Wichmann AB, Adang EM, Stalmeier PF, et al. The use of Quality-Adjusted Life Years in cost-effectiveness analyses in palliative care: Mapping the debate through an integrative review. *Palliat Med* 2017;31:306-22.
 43. Coast J, Bailey C, Kinghorn P. Patient centered outcome

- measurement in health economics: beyond EQ-5D and the Quality-Adjusted Life-Year-where are we now? *Ann Palliat Med* 2018;7:S249-52.
44. Rand SE, Malley JN, Netten AP, et al. Factor structure and construct validity of the Adult Social Care Outcomes Toolkit for Carers (ASCOT-Carer). *Qual Life Res* 2015;24:2601-14.
 45. Brouwer WB, van Exel NJ, van Gorp B, et al. The CarerQol instrument: a new instrument to measure care-related quality of life of informal caregivers for use in economic evaluations. *Qual Life Res* 2006;15:1005-21.
 46. Brazier J, Peasgood T, Mukuria C, et al. The EQ-HWB: Overview of the Development of a Measure of Health and Wellbeing and Key Results. *Value Health* 2022;25:482-91.
 47. Hutchinson C, Worley A, Khadka J, et al. Do we agree or disagree? A systematic review of the application of preference-based instruments in self and proxy reporting of quality of life in older people. *Soc Sci Med* 2022;305:115046.

Cite this article as: Gottschalk S, König HH, Mallon T, Schulze J, Weber J, Böttcher S, Sekanina U, Asendorf T, Hummers E, Freitag M, Schneider N, Friede T, Nauck F, Scherer M, Marx G, Dams J. Cost-effectiveness of a specialist palliative care nurse-patient consultation followed by an interprofessional case conference for patients with non-oncological palliative care needs: results of the KOPAL trial. *Ann Palliat Med* 2023;12(6):1175-1186. doi: 10.21037/apm-23-88

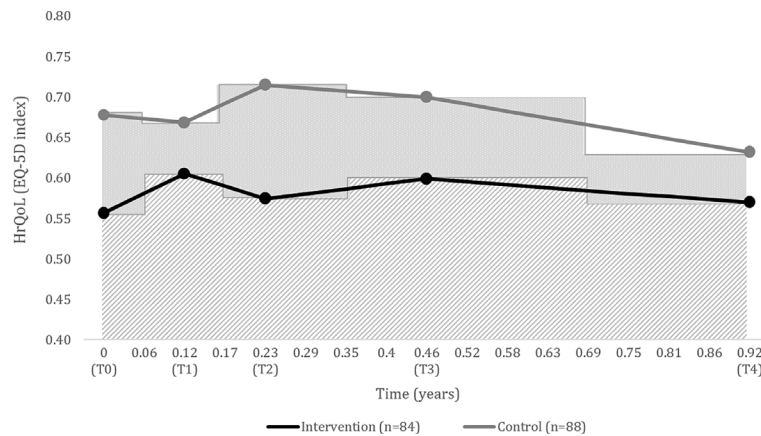


Figure S1 Mean EQ-5D indices at different follow-up time points by group (only participants still alive at the respective time point). Example of QALY calculation for the intervention group by determining the area under the curve (shaded area): $0.12 * ((0.56 + 0.61) / 2) + 0.12 * ((0.61 + 0.57) / 2) + 0.23 * ((0.57 + 0.60) / 2) + 0.46 * ((0.60 + 0.57) / 2) = 0.54$. The mean QALYs in this example do not match the mean QALYs reported in Table 3 because in Figure S1 the mean EQ-5D indices at the different follow-up time points are based on participants still alive at the respective time points, whereas for the value in Table 3 QALYs accumulated until death of the deceased participants were also taken into account. QALYs, quality-adjusted life years.

Table S1 Calculation of intervention costs (€)

| Intervention component | SPHC nurse | SPHC physician | General practitioner | Travel expenses | Sum |
|---|------------|----------------|----------------------|-----------------|------------|
| Consultation between patient and SPHC nurse (Ø 60 min) | 60 | | | 9 | 69 |
| Consultation between SPHC nurse and SPHC physician (Ø 5 min) | 5 | 10 | | | 15 |
| Case conference (SPHC nurse, SPHC physician, general practitioner) (Ø 18 min) | 18 | 36 | 36 | | 90 |
| Total intervention costs | | | | | 174 |

Ø, average. Assumptions: average hourly labour costs: SPHC nurse: €60, general practitioner/SPHC physician: €120; average travel expenses: €9. SPHC, specialist palliative home care.

Table S2 Costs (in 2020 euros) and QALYs at 24 weeks

| Category | Intervention (n=87) | Control (n=88) | Difference |
|---------------------|---------------------------|--------------------------|--------------------------|
| Outpatient services | 1,412 (801 to 2,024) | 1,534 (794 to 2,274) | -122 (-1,087 to 843) |
| Physician | 1,117 (516 to 1,719) | 1,204 (478 to 1,931) | -87 (-1,035 to 861) |
| Therapist | 295 (208 to 383) | 330 (191 to 469) | -35 (-201 to 131) |
| Formal support | 1,322 (820 to 1,825) | 2,033 (839 to 3,228) | -711 (-2,029 to 607) |
| Informal support | 28,266 (19,604 to 36,929) | 13,466 (7,731 to 19,201) | 14,801 (4,565 to 25,037) |
| Medical aids | 217 (95 to 340) | 319 (82 to 556) | -101 (-372 to 169) |
| Medications | 1,244 (996 to 1,492) | 1,112 (898 to 1,325) | 133 (-194 to 459) |
| QALY | 0.27 (0.24 to 0.3) | 0.32 (0.29 to 0.34) | -0.04 (-0.08 to -0.01) |

Data are presented as mean (95% CI). QALY, quality-adjusted life year; CI confidence interval.