Peer Review File

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Reviewer A

This manuscript presents a within-trial cost-effectiveness analysis of the KOPAL intervention, a structured palliative care nurse-patient consultation followed by an interprofessional telephone case conference by focusing on full economic costs of palliative care and not just cost savings and thereby shifting from a cost analysis approach to an evaluations of efficiency of palliative care.

The topic has practical relevance for decision making in policy and this is a valuable addition to the existing literature. The article is well written and easy to read. The problem is set out well, and the methods are described in detail on the whole. The results seem plausible and are supported by sensitivity analysis. The generated evidence is inconclusive but informative and provides a direction for future research.

I only have one specific comment:

Comment 1: The authors present the results at the follow up of 48 weeks. I am curious how the results looked at other follow-up time periods, especially T3 (24 weeks). If the authors conducted the analysis at multiple follow up time periods it will be worthwhile to share the general trend or detailed results as a supplement or as part of their sensitivity analysis.

Reply 1: Thank you for your general positive feedback on the manuscript. Regarding the results at other follow-up time points, an additional table reporting costs (outpatient services, formal/informal support, medical aids, medications) and QALYs at 24 weeks was prepared and included in the supplementary appendix (Table S1). Information on the use of inpatient services was only collected at T0 and T4 from the GP. Hence, it is not possible to calculate exact costs for the use of inpatient services until T3.

Table S1 Costs (in 2020 euros) and QALYs at24 weeks

	Mean (95% CI)		
	Intervention (n=87)	*Mean (95% CI) Control*	*Mean (95% CI) Difference*
Outpatient services	*1412 (801, 2024)*	*1534 (794, 2274)*	*-122 (-1087, 843)*
Physician	*1117 (516, 1719)*	*1204 (478, 1931)*	*-87 (-1035, 861)*
Therapist			
Formal support	*295 (208, 383)*	*330 (191, 469)*	*-35 (-201, 131)*
Informal support	*1322 (820, 1825)*	*2033 (839, 3228)*	*- 711 (-2029, 607)*
Medical aids	*28266 (19604, 36929)*	*13466 (7731, 19201)*	*14801 (4565,*

Medications	*217 (95, 340)*	*319 (82, 556)*	*25037)*
QALY	*1244 (996, 1492)*	*1112 (898, 1325)*	*-101 (-372, 169)*
	0.27 (0.24, 0.3)	*0.32 (0.29, 0.34)*	*133 (-194, 459)*
			-0.04 (-0.08, -0.01)

Abbreviations: CI= confidence interval, QALY= quality-adjusted life years

The following changes were made to the manuscript:

"*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 ofthe FIMA questionnaire for the use of medical and non-medical services in old age (25) (6 [T1, T2], 12 [T0, T3], or 24 weeks [T4] retrospectively). Information on inpatient services use (general/psychiatric hospitalisation and rehabilitation) was collected fromthe GP at T0 and T4 (48 weeks retrospectively).* " (page 7, line 153-159)

"*After 48weeks follow-up, […] The differences in formal and informal care costs between IG and CG remained, resulting in higher unadjusted total costs fromthe societal perspective (+€25 836, 95% CI [2 721, 48 952]) and lower total costs fromthe healthcare payer*

perspective (−€1 685, 95 % CI [−8 952, 5 582]) (Table 3; unadjusted mean costs and QALYs after 24 weeks are reported in Table S2, supplementary appendix). " (page 10, line 225-230)

Reviewer B

Many thanks for this interesting paper. You have highlighted many of the areas where conducting health economic analysis with this patient population is challenging.

Reply: Thank you for reviewing the manuscript and the general positive evaluation.

Comment 1: The main comment I have is whether a model-based approach would have been more useful with this patient group. This would allow extrapolation beyond the 48 weeks which would have been interesting. Does the intervention have any longer term gains for a patient? The results in the short term do not look promising but too little information is given to how the 4 QALY measurements
per person were used. It was assumed that the relationship is linear, some proof of this by diagram/summary statistics for QALYs at each individual time point would have been interesting.

See Adamson et al (2021) https://doi.org/10.1016/s2468-1253(21)00004-2, for a description on how to use modelling methodology.

Reply 1: In fact, it would be desirable to support long-term decisions, e.g. through modelling approaches. This is particularly important when an intervention shows benefits to care as usual. The present analysis is part of an RCT designed to evaluate a new intervention focusing on the management of outpatient palliative are and can be seen as a first step towards integration of the intervention into standard palliative care in Germany. Long-term data are unfortunately not yet available. An extrapolation of the results beyond the 48 weeks was refrained from, as extrapolation always depends on the available observational data, from which, for example, assumptions are made about the development of costs and effects beyond the observed period. Given the high uncertainty of the results after 48 weeks and the challenges described with regard to sample size, heterogeneity, etc., a solid data basis hardly seems to be given, so that further study data will be needed in order to be able to predict long- term cost and effects by study data and model-based approaches.

The paragraph describing the calculation of QALYs has been rephrased and extended. Mean EQ-5D indices by group and separate for different time points are now graphically presented by Figure S1 in the supplementary appendix. In addition, an exemplary calculation of QALYs is provided below the figure.

"QALYs were obtained as weighted linear combinations ofthe EQ-5D indices fromthe four follow-up assessment time points (compare supplementary appendix, 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. " (page 8, line 172-176)

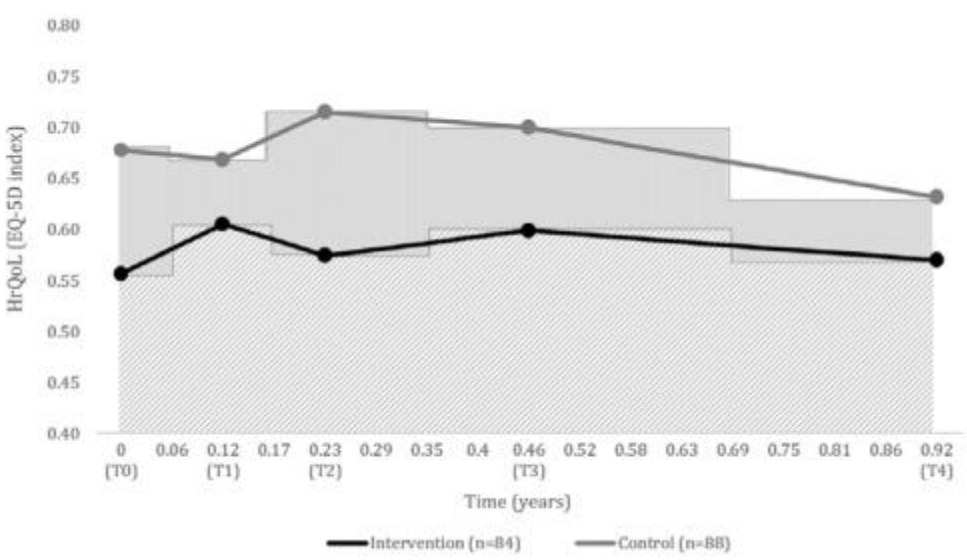

Figure S1 Mean EQ-5D indices at differentfollow-up time points by group (only participants still alive at the respective time point)

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*

Note: 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 differentfollow-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.

Comment 2: Also, you have not made any comments relating to the mortality of these patients, how many were still alive at 48 weeks? I would imagine that in a period of 48 weeks and a palliative care population that some patients may have passed away during this time. Some indication of mortality is essential to include in this paper.

Reply 2: The number of deaths in the period of 48 weeks in each group is now reported in Table 1 and in the results section:

"After 48weeks follow-up, 11 participants (13%) in the IG and 9 participants (10%) in the CG had died." (page 10, line 225)

Comment 3: I can see from Tables 2 and 3 that n is the same. You have commented on using Multiple Imputation to impute missing values where appropriate but if the patient has passed away this is not suitable, their QALY will be zero.

Reply 3: Participants who died were still included in the cost-effectiveness analysis, as this is a realistic case and these participants are still relevant for the analysis. If a participant died, health utility (EQ-5D index) and costs were set

to zero for the subsequent assessment time points. Therefore, the QALYs for these participants are not automatically zero (they were still alive for some time in the observation period with a non-zero health utility), but the survived time was of course taken into account when calculating the QALYs. Only missing data for reasons other than death and costs during the follow-up interval in which a participant died were imputed (e.g. for a participant who was assessed at T0 and T1 but died between T1 and T2, cost data were imputed for the period between T1 and T2, as the participant may have accumulated costs during this period until death). See reply to comment 1 regarding the changes made to the manuscript.