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BMJ Open

End-of-life care preferences of older patients with multimorbidity: protocol of a systematic review.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038682
Article Type:	Protocol
Date Submitted by the Author:	19-Mar-2020
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Keywords:	<p>GENERAL MEDICINE (see Internal Medicine), GERIATRIC MEDICINE, ETHICS (see Medical Ethics), INTERNAL MEDICINE, Adult palliative care < PALLIATIVE CARE</p>



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1 **TITLE**

2 End-of-life care preferences of older patients with multimorbidity: protocol of a systematic
3 review.

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76 **ABSTRACT**

77 **Introduction**

78 End-of-life care is an essential task performed by most health care providers, and often
79 involves decision-making about how and where patients want to receive care. To provide
80 decision support to health care professionals and patients in this difficult situation, we will
81 systematically review an evidence cluster on the end-of-life care preferences of older patients
82 with multimorbidity that we previously identified using an evidence map.

83 **Methods and analysis**

84 We will systematically search for studies reporting end-of-life care preferences of older
85 patients (mean age ≥ 60) with multimorbidity (≥ 2 chronic conditions) in MEDLINE, CINAHL,
86 PsycINFO, Social Sciences Citation Index, Social Sciences Citation Index Expanded, PSYINDEX
87 and The Cochrane Library from inception. We will include all primary studies that use
88 quantitative, qualitative and mixed methodologies, irrespective of publication date and
89 language.
90 Two independent reviewers will assess eligibility, extract data and describe evidence in terms
91 of study/population characteristics, preference assessment method, and end-of-life care
92 elements that matter to patients (e.g. life-sustaining treatments). Risk of bias/applicability of
93 results will be independently assessed by two reviewers using the Mixed Methods Appraisal
94 Tool. Using a convergent integrated approach on qualitative/quantitative studies, we will
95 synthesize information narratively and, wherever possible, quantitatively.

96 **Ethics and dissemination**

97 Due to the nature of the proposed systematic review, ethics approval is not required. Results
98 from our research will be disseminated at relevant (inter-)national conferences and via
99 publication in peer-reviewed journals. Synthesizing evidence on end-of-life care preferences of
100 older patients with multimorbidity will improve shared decision-making and satisfaction within
101 this final life period.

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- 102 **Registration**
- 103 Submitted to PROSPERO (receipt number 151862); assignment in progress.
- 104 Evidence map registration: Open Science Framework (OSF): DOI 10.17605/OSF.IO/MCRWQ.

For peer review only

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3 105 **Strengths and limitations of this study**
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5 106 A multinational and multidisciplinary team with considerable methodological experience and
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7 107 skills will provide the necessary expertise.
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11 108 A patient representative has been involved in designing the study to ensure that from the
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13 109 beginning, patient-relevant questions are assessed, and results discussed accordingly.
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17 110 The main study limitations are the poor indexing of articles, and the lack of or non-
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19 111 standardized definition of “patient preferences”.
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112 **INTRODUCTION**

113 Multimorbidity, or the presence of multiple coexisting diseases or conditions (1), affects the
114 majority of older adults (2), and is associated with increased mortality and health care
115 utilization (3–5). In addition, multimorbidity negatively impacts quality of life and increases
116 symptom burden (6–8). Evidence is therefore required on how to best manage multimorbid
117 patients (9, 10).

118 The care of patients with multimorbidity entails complex medical decision-making, especially
119 at the end of life (EoL). EoL care refers not only to the health care services that are provided to
120 patients in the final hours or days of their lives, but, more broadly, to those provided to all
121 patients whose conditions have become advanced, progressive, and incurable (11, 12). EoL
122 care must be embedded within the context of patient preferences, so the care multimorbid
123 patients receive during the final days of their lives is concordant with the care they desire. The
124 provision of effective EoL care to those with multimorbidity is impossible without cooperation
125 between health care providers from palliative care, specialty care and primary care. In fact,
126 EoL care is an essential task performed by most health care providers, and often involves
127 decision-making about how and where patients want to receive care.

128 According to recent studies that were not confined to patients with multimorbidity, most adult
129 patients’ EoL care preferences (e.g. for cardiopulmonary resuscitation) are stable over time
130 and independent of their health status (13). A systematic review of where adult patients would
131 prefer to die revealed that most people would prefer to die at home and that such preferences
132 are independent of changes in health status (14). These results were confirmed in another
133 systematic review (15) on adult patients with diverse health conditions. However, it was
134 unclear what proportion of patients preferred home when the underlying condition is taken
135 into account (e.g. cancer *versus* non-cancer conditions) (15). Furthermore, considerable
136 heterogeneity between and within population groups has been found, both in the proportion

137 of patients whose preferences change over time and in the direction of such changes (e.g.
138 towards or away from more aggressive care) (10, 13).
139 Multimorbidity is positively associated with the desire not to be resuscitated, but this finding
140 depends on the nature of the morbidities. Cognitive impairment, stroke and cancer were very
141 positively associated with the desire not to be resuscitated, while heart diseases were not (16).
142 However, we have no information on the preferences of patients with a mix of disabling / life-
143 threatening conditions or an accumulation of several conditions. To the best of our knowledge,
144 no systematic review has focused on EoL care preferences of older patients with
145 multimorbidity.
146 To provide decision support to health care providers and assist this complex patient
147 population in an emotionally difficult situation, we therefore aim to systematically review a
148 cluster of EoL care preferences of older patients with multimorbidity that we previously
149 identified in an evidence map we prepared on health-related preferences (17). This will allow
150 us to synthesize current knowledge of EoL care preferences and help prioritize and guide
151 future innovations in EoL care policy.

152

153 **METHODS AND ANALYSIS**

154 The present protocol will follow the Preferred Reporting System Items for Systematic Review
155 and Meta-Analysis Protocols (PRISMA-P) checklist (18) (see online additional file 1).

156 [About here link to: Additional file 1. Preferred Reporting System Items for Systematic Review
157 and Meta-Analysis Protocols (PRISMA-P) checklist]

158 **Design**

159 Mixed methods systematic review using the convergent integrated approach on qualitative /
160 quantitative study designs.

161 **Criteria for considering studies for this review**

162 ***Types of studies***

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We will include primary studies that use quantitative (e.g. questionnaires), qualitative (e.g. interviews, focus groups) and mixed methods methodologies.

We will exclude case reports and articles, such as conference abstracts, narrative reviews and editorials, that include no detailed description of methods.

Types of participants

We will include older patients (mean or median age ≥ 60 years) with multimorbidity (two or more simultaneous conditions) (1).

Studies addressing only the preferences of caregivers, family members, and health care professionals, will be excluded. Studies confined to population-based and general public perspectives will also be excluded.

Types of outcomes

Primary outcome

Our primary outcome will focus on patients' EoL care preferences with respect to i) the use or non-use of life-sustaining treatments (e.g. percentage of patients with preferences for or against cardiopulmonary resuscitation, intubation and mechanical ventilation, intensive care, intravenous nutritional support, nasogastric tube feeding and/or dialysis withdrawal), ii) palliation of symptoms and iii) the place where EoL care is to be administered (e.g. percentage of patients that would prefer to die at home).

We will leave out studies investigating preferences for or against interventions of limited availability or whose legal status is unclear (e.g. preferences for or against euthanasia or physician-assisted suicide, which is neither legal nor available in most Western countries). We will also exclude studies exploring patients' will to live.

Table 1. Inclusion & exclusion criteria

Inclusion criteria	Exclusion criteria

<p>⇒ Quantitative (observational & interventional) and qualitative studies addressing end-of-life care preferences from the patient's perspective</p> <p>⇒ Age: average/median age of 60 or older, geriatric patients, elderly patients</p> <p>⇒ Multimorbidity: two or more simultaneous acute or chronic conditions</p> <p>⇒ Setting: We will not apply restrictions to geographical location, country or healthcare context</p> <p>⇒ No restrictions to the date of publication or language of the study</p>	<p>⇒ Case reports</p> <p>⇒ Articles without details of methods</p> <ul style="list-style-type: none"> ○ Conference abstracts ○ Narrative reviews ○ Editorials <p>⇒ Studies investigating preferences for or against interventions that are not generally available or only legal in limited contexts (e.g. euthanasia)</p> <p>⇒ Studies addressing only preferences of caregivers, family members and health care professionals</p> <p>⇒ Population-based studies (public health perspective)</p>
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187 Search methods used to identify studies

188 *Electronic searches*

189 We will search the following electronic sources from inception using a combination of MESH
 190 headings and keywords: MEDLINE, CINAHL, PsycINFO, Social Sciences Citation Index, Social
 191 Sciences Citation Index Expanded, PSYINDEX and The Cochrane Library. We will not apply any
 192 restrictions to publication date or language.

193 We will follow the recommendations of PRESS Peer Review of Electronic Search Strategies and
 194 develop the final search strategy in collaboration with an expert medical science librarian (19).

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3 195 The electronic search strategy for the MEDLINE database is provided in Table 2. This search
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5 196 strategy will be adapted for use in the other databases.
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7 197 [About here: Table 2. Search for End-of-Life Care Preferences]
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10 198 ***Searching other resources***
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12 199 We will identify potentially eligible studies that are not captured by our electronic database
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14 200 searches by examining the reference lists of included studies, relevant systematic reviews and
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16 201 meta-analyses, and by carrying out searches of cited references (forward and backward
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18 202 citation tracking) using the Web of Science Core Collection.
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21 203 ***Study records***
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23 204 ***Data management***
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25 205 Bibliographic details of all identified references will first be uploaded to Endnote© and then
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27 206 converted into COVIDENCE© for title, abstract and full text screening. Duplicates will be
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29 207 removed.
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32 208 ***Selection of studies***
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34 209 Two review authors (AIG, JN) will independently screen the title and abstract of every identified
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36 210 study to determine which should be assessed further. Before screening, a stepwise calibration
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38 211 exercise will be performed on a sample of 30 studies (20), with the aim of achieving 80%
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40 212 agreement between reviewers. In case 80% agreement is not reached, our inclusion and
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42 213 exclusion criteria will be refined, and the calibration repeated until the threshold is met. We will
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44 214 report any changes to the inclusion and exclusion criteria that result from the calibration
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46 215 exercise as deviations from the published protocol. The full text of potentially eligible papers
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48 216 will be then retrieved and independently assessed for eligibility by two reviewers (AIG, JN). Any
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50 217 discrepancy will be resolved through discussion and consensus (CS).
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53 218 We will present a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)
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55 219 flow-chart of study selection (21).
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58 220 ***Data collection***
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221 Two review authors (AIG, JN) will independently extract key study and participant
 222 characteristics from all studies that fulfil the inclusion criteria, and report data on outcomes.
 223 Any disagreement will be resolved by discussion, or by a third author (CS), if necessary. A
 224 calibration process similar to the one described above will precede data extraction.

225 ***Data items***

226 We will stratify data extraction according to study type. Using standard extraction templates in
 227 Access datasheets, data will be extracted under the following headings: i) *Study reference* (i.e.
 228 first author, year of publication, country of study origin); ii) *Study aim*; iii) *Study setting*; iv)
 229 *Sample size*; v) *Population characteristics* (e.g. age, sex, definition of multimorbidity, patient
 230 prognosis or illness severity, cancer or non-malignant condition); vi) *Preference-assessment*
 231 *method* (e.g. interview or questionnaire, number of assessments, time between assessments if
 232 applicable); vii) *Context of preference* (i.e. hypothetical / real, preference-sensitive situation);
 233 viii) *Information provided by the authors on the presentation of alternatives* (e.g. negative or
 234 positive framing (22, 23)); ix) *Outcome description* (EoL care elements that patients were
 235 queried about, e.g. resuscitation preference); and x) *Results of described outcomes* (e.g.
 236 proportion of participants expressing a preference for a specific type of EoL care) (Table 3).
 237 [About here: Table 3. Data extraction framework]

238 ***Dealing with duplicate and associated publications***

239 In the event of multiple reports (publications) of a primary study, we will maximize the yield of
 240 information by collating all available data and using the most complete dataset, aggregated
 241 across all known publications.

242 ***Assessment of risk of bias in included studies***

243 Two review authors (AIG, JN) will use the Mixed Methods Appraisal Tool (MMAT) and
 244 independently assess the risk of bias (RoB) and the applicability of the results for each included
 245 study (24). Assessments will be compared, and disagreements resolved through discussion and

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246 consensus, or by consultation with a third author if necessary (CS). If appropriate, sensitivity
247 analysis will be performed based on the results of the RoB evaluation.

248 **Data synthesis**

249 Should the included study pool permit quantitative information synthesis, we will conduct a
250 mixed methods systematic review using a convergent integrated approach that i) synthesizes
251 qualitative data by means of thematic synthesis, ii) synthesizes quantitative data, and
252 performs meta-analysis if applicable, and in a final step, iii) synthesizes both i) and ii) following
253 the methodology described by Sandelowski et al. and Pearson et al. (25, 26).
254 Descriptive analyses will be carried out if a lack of studies makes meta-analyses unfeasible, or
255 if heterogeneity prevents quantitative information synthesis. We will first assess heterogeneity
256 qualitatively (in terms of study design, population and outcomes). Assuming the qualitative
257 assessment does not preclude meta-analyses of studies, we will also assess heterogeneity by
258 means of X² and additional tests.

259 ***Planned sensitivity and subgroup analysis***

260 Sensitivity analyses are planned (irrespective of the presence of heterogeneity) to determine
261 the impact of bias by excluding studies that carry a high risk of it. If the study data allows, we
262 plan to conduct subgroup analyses to examine whether EoL care preferences are affected by
263 age, sex, specific life-sustaining treatment modalities, specific contexts of the preference
264 assessment (hypothetical or real scenarios), type of advanced disease (cancer or non-
265 malignant), patient prognosis or illness severity.

266 **Timeline for review**

267 At the time of this submission we have already completed electronic searches, piloted the
268 study selection process and started formally screening search results with respect to the
269 eligibility criteria. This systematic review is scheduled to end in August 2020.

270 **Patient and public involvement**

271 A patient representative (KR) from the Federal Joint Committee “Gemeinsamer
272 Bundesausschuss (G-BA)” actively participated in the design of the systematic review. KR has
273 considerable experience in evidence-based medicine and an understanding of the pivotal role
274 of patients’ preferences in the provision of health care. The G-BA is the ultimate decision-
275 making body for the joint self-administration of stakeholders in the German health service,
276 and the statutory health insurance service catalogue for over 70 million insured individuals is
277 based on its guidelines.

278

279 **ETHICS AND DISSEMINATION**

280 Due to the nature of the proposed systematic review, ethics approval is not required. We will
281 disseminate our study findings to health care providers and patients, and present them at
282 relevant national and international conferences. We also aim to publish the results of the
283 study in a peer-reviewed journal.

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30 352 **DECLARATIONS**

32 353 **Authors’ contributions**

34 354 AIG wrote the initial draft of the protocol. CM is the guarantor of the review. CS and JJM
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38 356 identification of databases and reviewed the search strategy. TSN, MSB, JWB, MvdA, KR, OW,
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42 358 development of the protocol, and contributed to the revision of the manuscript. All authors
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46 360 **Acknowledgements**

48 361 The authors would like to thank Kiran Chapidi for his support as data manager.

50 362 **Funding statement**

52 363 This work was supported by the German Federal Ministry of Education and Research, grant
53
54 364 number 01GL1729. The funder had no role in developing the protocol for this review.

56 365 **Competing interests**

366 The authors declare that they have no competing interests.

367 **Ethics approval and consent to participate**

368 Not applicable

369 **Consent for publication**

370 Not applicable

371 **Availability of data and materials**

372 All data to be generated or analyzed during this study are included in the published article [and
373 its supplementary information files].

374 **Word count**

375 1,871

Table 2. Search for End-of-Life Care Preferences

13.09.2019 – Medline via Ovid (medall)

1.	((advanced OR incurabl* OR progressive OR life-limiting OR fatal OR serious* OR end-stage OR terminal*) adj3 (disease OR condition OR illness OR ill OR morbid*)).ti,ab,kf.	End-of-Life
2.	(End of life OR (last days adj3 life) OR (last year* adj3 life) OR (last week* adj3 life) OR (last month* adj3 life) OR (last days adj3 live) OR (last week* adj3 live) OR (last month* adj3 live) OR (last year* adj3 live) OR imminent death OR (close adj3 death) OR before death OR palliative).ti,ab,kf.	End-of-life
3.	(Terminal Care OR Terminally Ill OR Hospice Care OR Life Support Care OR Advanced Cardiac Life Support OR Palliative Care).sh.	
4.	or/1-3	
5.	(Comorbidity OR Multimorbidity OR Multiple Chronic Conditions).sh.	Multimorbidity
6.	((comorbid* OR multiple OR several OR multi OR concurrent OR complex OR more than one) adj4 (disease* OR condition* OR illness* OR morbid*)).ti,ab,kf.	
7.	(Comorbidit* OR multimorbidit* OR multidisease* OR polymorbid* OR frail*).ti,ab,kf.	
8.	or/5-7	

9.	4 AND 8	
10.	(scale OR scaling OR ranking OR rating OR conjoint-analysis OR conjoint-analyses OR contingent valuation OR analytic hierarch* process* OR time trade off OR evidential reasoning OR multi-attribute utility OR maut OR multiattribute decision model OR madm OR electre iv OR electre is OR visual analog* scale OR score* OR scoring OR standard gamble OR EVIDEM OR paprika method OR simple additive weighting method OR weighted product method OR wpm OR technique for order preference by similarity to ideal solution OR topsis OR analytic network process OR anp OR todim OR macbeth OR smart OR focus group* OR interview* OR questionnaire* OR choice).ti,ab,kf.	Methods to elicit Preferences
11.	(prefer* OR wish* OR need OR needs OR value* OR belief* OR want* OR desire* OR priorit* OR attitude* OR perception* OR evaluation* OR choice* OR experience* OR decision* OR decide* OR perspective*).ti,ab,kf.	Preferences
12.	(patient* OR women* OR men* OR elder* OR old* OR frail*).ti,ab,kf.	
13.	10 AND 11 AND 12	

14.	(Patient Satisfaction OR Patient Preference OR Health Priorities OR Needs Assessment OR Advance Care Planning OR Advance Directives).sh.	
15.	9 AND 13	
16.	9 AND 14	
17.	or/15-16	2,176 articles retrieved

Table 3. Data extraction framework

Bibliometrics	Description	Coding
Study identification	First Author, year of publication	(journal's description)
Study characteristics	Study aim	(authors' description)
	Geographical location	Country
	Study setting	Inpatient, outpatient
	Type of study	Observational (i.e. qualitative, quantitative cross-sectional, quantitative longitudinal, mixed methods) or interventional study
Patient characteristics	Sample size	Number of patients
	Age	(years)
	Sex	(% females)
	Definition of multimorbidity	(authors' description)
	Prognosis or illness severity indices (if applicable)	e.g. less than 6 months of life or congestive heart failure NYHA II-IV
	Type of index condition (if applicable)	Cancer or non-malignant
Methods of data collection	Type of data collection	Interview, semi-structured interview, survey, focus

		group, questionnaire (authors' description)
	Context of the preference	Hypothetical / real preference-sensitive situation*
	Presentation of information on alternatives – Framing effect**	High-risk of positive-negative framing, low risk of framing or unclear
	Number of assessments	e.g. one assessment if cross- sectional, two or more assessments if longitudinal
	Time between assessments	If applicable
Outcome	Outcome description	Type of EoL preference queried e.g. cardiopulmonary resuscitation
	Outcome results	e.g. percentage of patients for or against life-sustaining treatments (number of patients stating a preference out of all the patients included in the study)
Results / Conclusions		(authors' description)

EoL = End of Life; NYHA = New York Heart Association.

*Hypothetical preference-sensitive situation: EoL care preferences are measured by asking study participants to imagine themselves in a situation in the future that requires such care;

Real preference-sensitive situation: EoL care preferences are measured by asking study participants to state their preferences in a context that actually requires them to express a preference for such care. Examining preferences using hypothetical scenarios removes the acute stress of making decisions when confronted with an EoL situation.

**Framing effect: Cognitive bias caused by the influence of the way information is presented on the choices people make.

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PRISMA-P 2015 Checklist

5 This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting

6 items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

7

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	102-104
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	5-75
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	353-359
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input type="checkbox"/>	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	362-364
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	362-364
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	362-364
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	112-145
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	146-151

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	162-186 Table 1
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	187-192
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	195-197 Table 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	204-207
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	208-219
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	220-224
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	225-237 Table 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	235-237 Table 3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	242-247
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	248-258
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	248-258
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	259-265
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	248-258

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	259-261
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	242-247

NA = not applicable

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BMJ Open

End-of-life care preferences of older patients with multimorbidity: protocol of a mixed-methods systematic review.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038682.R1
Article Type:	Protocol
Date Submitted by the Author:	19-May-2020
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Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	General practice / Family practice, Palliative care
Keywords:	GENERAL MEDICINE (see Internal Medicine), GERIATRIC MEDICINE, ETHICS (see Medical Ethics), INTERNAL MEDICINE, Adult palliative care < PALLIATIVE CARE



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1 **TITLE**

2 End-of-life care preferences of older patients with multimorbidity: protocol of a mixed-
3 methods systematic review.

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75 **ABSTRACT**

76 **Introduction**

77 End-of-life care is an essential task performed by most health care providers, and often
78 involves decision-making about how and where patients want to receive care. To provide
79 decision support to health care professionals and patients in this difficult situation, we will
80 systematically review a knowledge cluster of the end-of-life care preferences of older patients
81 with multimorbidity that we previously identified using an evidence map.

82 **Methods and analysis**

83 We will systematically search for studies reporting end-of-life care preferences of older
84 patients (mean age ≥ 60) with multimorbidity (≥ 2 chronic conditions) in MEDLINE, CINAHL,
85 PsycINFO, Social Sciences Citation Index, Social Sciences Citation Index Expanded, PSYINDEX
86 and The Cochrane Library from inception to September 2019. We will include all primary
87 studies that use quantitative, qualitative and mixed methodologies, irrespective of publication
88 date and language.

89 Two independent reviewers will assess eligibility, extract data and describe evidence in terms
90 of study/population characteristics, preference assessment method, and end-of-life care
91 elements that matter to patients (e.g. life-sustaining treatments). Risk of bias/applicability of
92 results will be independently assessed by two reviewers using the Mixed-Methods Appraisal
93 Tool. Using a convergent integrated approach on qualitative/quantitative studies, we will
94 synthesize information narratively and, wherever possible, quantitatively.

95 **Ethics and dissemination**

96 Due to the nature of the proposed systematic review, ethics approval is not required. Results
97 from our research will be disseminated at relevant (inter-)national conferences and via
98 publication in peer-reviewed journals. Synthesizing evidence on end-of-life care preferences of
99 older patients with multimorbidity will improve shared decision-making and satisfaction in this
100 final period of life.

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- 101 **Registration**
- 102 PROSPERO registration number: CRD42020151862.

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3 103 **Strengths and limitations of this study**
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5 104 This is the first systematic review on end-of-life care preferences of patients with
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7 105 multimorbidity and will provide an important body of evidence to support the consideration of
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9 106 patient-centred care in end-of-life care policy.
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13 107 A multinational and multidisciplinary team with considerable methodological experience and
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15 108 skills will provide the necessary expertise.
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19 109 A patient representative has been involved in designing the study to ensure that from the
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21 110 beginning, patient-relevant questions are assessed, and results discussed accordingly.
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24 111 The main study limitations are the poor indexing of articles, and the missing or non-
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26 112 standardized definition of “patient preferences”.
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113 **INTRODUCTION**

114 Multimorbidity, or the presence of multiple coexisting chronic diseases or conditions (1),
115 affects the majority of older adults (2), and is associated with increased mortality and health
116 care utilization (3–5). In addition, multimorbidity negatively impacts quality of life and
117 increases symptom burden (6–8). Evidence is therefore required on how to best manage
118 multimorbid patients (9, 10).

119 The care of patients with multimorbidity entails complex medical decision-making, especially
120 at the end of life (EoL). EoL care refers not only to the health care services that are provided to
121 patients in the final hours or days of their lives, but, more broadly, to those provided to all
122 patients whose conditions have become advanced, progressive, and incurable (11, 12). EoL
123 care must be embedded within the context of patient preferences, so the care multimorbid
124 patients receive during the final days of their lives is concordant with the care they desire.

125 However, individuals with multimorbidity often have to make numerous and conflicting
126 decisions and choices, which makes eliciting their preferences rather challenging. The
127 provision of effective EoL care to those with multimorbidity is impossible without cooperation
128 between palliative care providers, specialty care, and primary care. In fact, EoL care is an
129 essential task performed by most health care providers, and often involves decision-making
130 about how and where patients want to receive care.

131 According to recent studies that were not confined to patients with multimorbidity, most
132 adults’ EoL care preferences (e.g. for cardiopulmonary resuscitation) are stable over time and
133 independent of their health status (13). A systematic review of where adult patients would
134 prefer to die revealed that most people would prefer to die at home and that such preferences
135 are independent of changes in health status (14). These results were confirmed in another
136 systematic review (15) on adults with diverse health conditions. However, it was unclear what
137 proportion of people preferred home when the underlying condition was taken into account
138 (e.g. cancer *versus* non-cancer conditions) (15). Furthermore, considerable heterogeneity

139 between and within population groups exists, both in the proportion of patients whose
140 preferences change over time and in the direction of such changes (e.g. towards or away from
141 more aggressive care) (10, 13).

142 Multimorbidity is positively associated with the desire not to be resuscitated, but this finding
143 depends on the nature of the morbidities. Cognitive impairment, stroke and cancer were very
144 positively associated with the desire not to be resuscitated, while heart diseases were not (16).
145 However, we have no information on the preferences of patients with a mix of disabling / life-
146 threatening conditions or an accumulation of several conditions. To the best of our knowledge,
147 no systematic review has focused on EoL care preferences of older patients with
148 multimorbidity.

149 To provide decision support to health care providers and assist this complex patient
150 population in an emotionally difficult situation, we aim to systematically review EoL care
151 preferences of older patients with multimorbidity. We will base the review on a knowledge
152 cluster of EoL care preferences that we identified in an evidence map we previously developed
153 on health-related preferences in older patients with multimorbidity (17). The systematic
154 review is the natural next step and will allow us to synthesize current knowledge of EoL care
155 preferences and help prioritize and guide future innovations in EoL care policy.

156

157 **METHODS AND ANALYSIS**

158 The present protocol will follow the Preferred Reporting System Items for Systematic Review
159 and Meta-Analysis Protocols (PRISMA-P) checklist (18) (see online additional file 1).

160 [About here link to: Additional file 1. Preferred Reporting System Items for Systematic Review
161 and Meta-Analysis Protocols (PRISMA-P) checklist]

162 **Design**

1
2
3 163 Mixed-methods systematic review using the convergent integrated approach in which data is
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5 164 transformed in such a way that quantitative and qualitative data can be combined, and the
6
7 165 synthesis of quantitative and qualitative studies simultaneously occurs (19).
8

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10 166 **Criteria for considering studies for this review**

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12 167 ***Types of studies***

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14 168 We will include primary studies that use quantitative (e.g. questionnaires), qualitative (e.g.
15
16 169 interviews, focus groups) and mixed-methods methodologies. Systematic reviews and meta-
17
18 170 analyses will not be included, but if a systematic review is relevant to our topic we will screen
19
20 171 its reference list for potentially eligible studies that were not identified in our systematic
21
22 172 literature searches (see the section on search methods used to identify studies).
23

24
25 173 We will exclude case reports and articles, such as conference abstracts, narrative reviews and
26
27 174 editorials.
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29
30 175 ***Types of participants***

31
32 176 We will include older patients (mean or median age ≥ 60 years (20)) with multimorbidity (two
33
34 177 or more simultaneous chronic conditions) (1). Studies focusing on patients with one chronic
35
36 178 disease will be included when authors have reported on at least one additional chronic
37
38 179 condition in the majority of the study population.
39

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41 180 Studies addressing only the preferences of caregivers, family members, and health care
42
43 181 professionals, will be excluded. Studies confined to population-based and general public
44
45 182 perspectives will also be excluded.
46

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48 183 ***Phenomenon of interest***

49
50 184 Our phenomenon of interest will focus on EoL care preferences, defined as preferences related
51
52 185 to the care that should be provided in the final period of life, regardless of whether it may, in
53
54 186 some cases, be provided for months or even years (12). EoL care preferences will comprise i)
55
56 187 willingness to receive life-sustaining treatments (e.g. percentage of people with preferences
57
58 188 for or against cardiopulmonary resuscitation, intubation and mechanical ventilation, intensive
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care, intravenous nutritional support, nasogastric tube feeding and/or dialysis withdrawal), ii) willingness to opt for palliation of symptoms, iii) the place where patients would prefer to receive EoL care (e.g. percentage of people that would prefer to die at home), and iv) interest in participating in a shared decision-making process related to EoL care.

We will exclude studies investigating preferences for or against interventions of limited availability or whose legal status is unclear (e.g. preferences for or against euthanasia or physician-assisted suicide) as such approaches are deemed outside the scope of this review.

We will also exclude studies exploring patients' will to live.

(see Table 1)

Table 1. Inclusion & exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ⇒ Quantitative (observational & interventional) and qualitative studies addressing end-of-life care preferences from the patient's perspective ⇒ Age: average/median age of 60 or older, geriatric patients, elderly patients ⇒ Multimorbidity: two or more simultaneous chronic conditions 	<ul style="list-style-type: none"> ⇒ Case reports ⇒ Articles without details of methods <ul style="list-style-type: none"> ○ Conference abstracts ○ Narrative reviews ○ Editorials ⇒ Studies investigating preferences for or against interventions that are not generally available or only legal in limited contexts (e.g. euthanasia) ⇒ Studies only addressing preferences of caregivers, family members and health care professionals

<p>⇒ Setting: We will not apply restrictions to geographical location, country or healthcare context</p> <p>⇒ No restrictions to the date of publication or language of the study</p>	<p>⇒ Population-based studies (public health perspective)</p>
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Search methods used to identify studies

Electronic searches

We will search the following electronic sources from inception using a combination of MESH headings and keywords: MEDLINE, CINAHL, PsycINFO, Social Sciences Citation Index, Social Sciences Citation Index Expanded, PSYINDEX and The Cochrane Library. To avoid publication bias, we will not apply any restrictions to publication date or language.

We will follow the recommendations of PRESS Peer Review of Electronic Search Strategies and develop the final search strategy in collaboration with an expert medical science librarian (21).

The electronic search strategy for the MEDLINE database from inception to September 2019 is provided in Table 2. This search strategy will be adapted for use in the other databases.

[About here: Table 2. Search for End-of-Life Care Preferences]

Searching other resources

We will identify potentially eligible studies that are not captured by our electronic database searches by examining the reference lists of included studies, relevant systematic reviews and meta-analyses, and by carrying out searches of cited references (forward and backward citation tracking) using the Web of Science Core Collection.

Study records

Data management

218 Bibliographic details of all identified references will first be uploaded to Endnote© and then
219 converted into COVidence© for title, abstract and full text screening. Duplicates will be
220 removed.

221 ***Selection of studies***

222 Each of the two review authors (AIG, JN) will independently screen the title and abstract of
223 each identified study to determine which should be assessed further. Before screening, a
224 stepwise calibration exercise will be performed on a sample of 30 studies (22), with the aim of
225 achieving 80% agreement between reviewers. In case 80% agreement is not reached, our
226 inclusion and exclusion criteria will be refined, and the calibration repeated until the threshold
227 is met. We will report any changes to the inclusion and exclusion criteria that result from the
228 calibration exercise as deviations from the published protocol. The full text of potentially
229 eligible papers will then be retrieved and independently assessed for eligibility by two
230 reviewers (AIG, JN). Any discrepancy will be resolved through discussion and consensus (CS).
231 We will present a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)
232 flow-chart of study selection (23).

233 ***Data collection***

234 One review author (AIG) will extract key study and participant characteristics from all studies
235 that fulfil the inclusion criteria, and report data on the phenomenon of interest. The second
236 review author (CS) will cross-check the extracted data. Any disagreement will be resolved by
237 discussion, or, if necessary, by a third author (CM).

238 ***Data items***

239 We will stratify data extraction according to study type. Using standard extraction templates in
240 Access datasheets, data will be extracted under the following headings: *Study reference* (i.e.
241 first author, year of publication, country of study origin); *Study aim*; *Study setting*; *Sample size*;
242 *Population characteristics* (e.g. age, sex, definition of multimorbidity, prognosis or illness
243 severity, cancer or non-malignant condition); *Preference-assessment method* (e.g. interview or

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3 244 questionnaire, number of assessments, time between assessments if applicable); *Context of*
4
5 245 *preference* (i.e. hypothetical / real, preference-sensitive situation); *Information provided by the*
6
7 246 *authors on the presentation of alternatives* (e.g. negative or positive framing (24, 25);
8
9 247 *Description of phenomenon of interest* (EoL care elements that study participants were queried
10
11 248 about, e.g. resuscitation preference); and *Results concerning the described phenomenon of*
12
13 249 *interest* (e.g. proportion of participants expressing a preference for a specific type of EoL care)
14
15 250 (Table 3).
16
17 251 [About here: Table 3. Data extraction framework]
18
19 252 ***Dealing with duplicate and associated publications***
20
21 253 In the event of multiple reports (publications) of a primary study, we will maximize the yield of
22
23 254 information by collating all available data and using the most complete dataset, aggregated
24
25 255 across all known publications.
26
27 256 ***Assessment of risk of bias in included studies***
28
29 257 A risk of bias assessment will be conducted using the Mixed-Methods Appraisal Tool (MMAT)
30
31 258 (26), whereby one author (AIG) will apply the MMAT criteria and a second author (CS) will verify
32
33 259 the assessments. Both authors will discuss the impact of the RoB assessments on further
34
35 260 analyses and involve a third author (CM) in cases of dissent. If an important RoB is detected,
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37 261 sensitivity analyses will be performed that exclude studies with a high RoB.
38
39 262 **Data synthesis**
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41 263 We will conduct a mixed-methods systematic review using a convergent integrated approach
42
43 264 in accordance with Joanna Briggs Institute methodology (19) that will i) synthesize qualitative
44
45 265 data by means of thematic synthesis, ii) synthesize quantitative data, and perform meta-
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47 266 analysis if applicable, and in a final step, iii) synthesize and integrate both i) and ii) following
48
49 267 the methodology described by Sandelowski et al. and Pearson et al. (27, 28). More specifically,
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51 268 the approach will include the following steps:
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269 i) Qualitative analysis and synthesis: Both reviewers (AIG, CS) will independently analyse
270 the extracted data and provide thematic codes. In order to derive a matrix structure,
271 both reviewers will discuss coding and identify overarching thematic issues and
272 categories with the help of MaxQDA18© software (29, 30).

273 ii) Quantitative analysis: Data from interventional and observational studies will be
274 analysed separately. The meta-analysis of data will be considered in studies that have
275 provided comparable and sufficiently homogeneous outcomes. We will first assess
276 heterogeneity qualitatively (in terms of study design, population and the phenomenon
277 of interest). Assuming the qualitative assessment does not preclude meta-analyses of
278 studies, we will also assess heterogeneity by means of X^2 and additional tests. If a
279 meta-analysis is impossible, a descriptive analysis will be carried out.

280 iii) Mixed-methods data synthesis (integrated synthesis methodology (27, 28)): To
281 synthesize qualitative and quantitative data, three reviewers (AIG, CS, CM) will decide
282 which is the most promising compatible format based on the results of i) and ii),
283 whereby the decision will depend mainly on the number of qualitative and
284 quantitative studies that are eligible for inclusion (27, 28)). Afterwards (27), data will
285 either be classified according to subject matter (resulting in data synthesis by means of
286 meta-aggregation), or by converting qualitative data into a numerical format (resulting
287 in a quantitative synthesis using meta-analytical approaches) (31, 32, 28).

288 ***Planned sensitivity and subgroup analysis***

289 If the available data allows, we will conduct sensitivity analyses that exclude studies at high
290 risk of bias in order to determine its impact. In addition, we plan to conduct subgroup analyses
291 to examine whether EoL care preferences are affected by sex, specific preference assessment
292 contexts (hypothetical or real scenarios), the type of advanced disease (cancer or non-
293 malignant) and patient prognosis or illness severity. If the included studies do not permit

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294 quantitative synthesis, we will descriptively report on evidence relating to the above-
295 mentioned aspects.

296 **Timeline for review**

297 At the time of this submission we have already completed electronic searches, piloted the
298 study selection process and started formally screening search results with respect to the
299 eligibility criteria. This systematic review is scheduled to end in August 2020.

300 **Patient and public involvement**

301 A patient representative (KR) from the Federal Joint Committee “Gemeinsamer
302 Bundesausschuss (G-BA)” actively participated in the design of the systematic review. He was
303 involved in defining the research question, selecting the methodology to be used and the data
304 to be collected, as well as selecting the phenomenon of interest. KR will also be involved in the
305 analysis and interpretation of the findings, crafting the overall message, the development of
306 recommendations and in the dissemination of the results. KR has considerable experience in
307 evidence-based medicine and an understanding of the pivotal role of patients’ preferences in
308 the provision of health care. The G-BA is the ultimate decision-making body for the joint self-
309 administration of stakeholders in the German health service, and the statutory health
310 insurance service catalogue for over 70 million insured individuals is based on its guidelines.

311

312 **ETHICS AND DISSEMINATION**

313 Due to the nature of the proposed systematic review, ethics approval is not required. We will
314 disseminate our study findings to health care providers and patients, and present them at
315 relevant national and international conferences. We also aim to publish the results of the
316 study in a peer-reviewed journal.

317

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42 404 **DECLARATIONS**

43
44 405 **Authors’ contributions**

45
46 406 AIG wrote the initial draft of the protocol. CM is the guarantor of the review. CS and JJM
47
48 407 provided methodological guidance and revisions of the manuscript. CS and JN assisted in the
49
50 408 identification of databases and reviewed the search strategy. TSN, MSB, JWB, MvdA, KR, OW,
51
52 409 TH, SES and FMG are co-supervisors of this project, provided advice at all stages of the
53
54 410 development of the protocol, and contributed to the revision of the manuscript. All authors
55
56 411 read and approved the final manuscript.
57
58
59

60 412 **Acknowledgements**

413 The authors would like to thank Kiran Chapidi for his support as data manager. We would also
414 like to thank Phillip Elliott for editing the manuscript.

415 **Funding statement**

416 This work was supported by the German Federal Ministry of Education and Research, grant
417 number 01GL1729. The funder had no role in developing the protocol for this review.

418 **Competing interests**

419 The authors declare that they have no competing interests.

420 **Ethics approval and consent to participate**

421 Not applicable

422 **Consent for publication**

423 Not applicable

424 **Availability of data and materials**

425 All data to be generated or analysed during this study are included in the published article [and
426 its supplementary information files].

427 **Word count**

428 2,284

Table 2. Search for End-of-Life Care Preferences

13.09.2019 – Medline via Ovid (medall)

1.	((advanced OR incurabl* OR progressive OR life-limiting OR fatal OR serious* OR end-stage OR terminal*) adj3 (disease OR condition OR illness OR ill OR morbid*)).ti,ab,kf.	End-of-Life
2.	(End of life OR (last days adj3 life) OR (last year* adj3 life) OR (last week* adj3 life) OR (last month* adj3 life) OR (last days adj3 live) OR (last week* adj3 live) OR (last month* adj3 live) OR (last year* adj3 live) OR imminent death OR (close adj3 death) OR before death OR palliative).ti,ab,kf.	End-of-life
3.	(Terminal Care OR Terminally Ill OR Hospice Care OR Life Support Care OR Advanced Cardiac Life Support OR Palliative Care).sh.	
4.	or/1-3	
5.	(Comorbidity OR Multimorbidity OR Multiple Chronic Conditions).sh.	Multimorbidity
6.	((comorbid* OR multiple OR several OR multi OR concurrent OR complex OR more than one) adj4 (disease* OR condition* OR illness* OR morbid*)).ti,ab,kf.	
7.	(Comorbidit* OR multimorbidit* OR multidisease* OR polymorbid* OR frail*).ti,ab,kf.	
8.	or/5-7	

9.	4 AND 8	
10.	(scale OR scaling OR ranking OR rating OR conjoint-analysis OR conjoint-analyses OR contingent valuation OR analytic hierarch* process* OR time trade off OR evidential reasoning OR multi-attribute utility OR maut OR multiattribute decision model OR madm OR electre iv OR electre is OR visual analog* scale OR score* OR scoring OR standard gamble OR EVIDEM OR paprika method OR simple additive weighting method OR weighted product method OR wpm OR technique for order preference by similarity to ideal solution OR topsis OR analytic network process OR anp OR todim OR macbeth OR smart OR focus group* OR interview* OR questionnaire* OR choice).ti,ab,kf.	Methods to elicit Preferences
11.	(prefer* OR wish* OR need OR needs OR value* OR belief* OR want* OR desire* OR priorit* OR attitude* OR perception* OR evaluation* OR choice* OR experience* OR decision* OR decide* OR perspective*).ti,ab,kf.	Preferences
12.	(patient* OR women* OR men* OR elder* OR old* OR frail*).ti,ab,kf.	
13.	10 AND 11 AND 12	

14.	(Patient Satisfaction OR Patient Preference OR Health Priorities OR Needs Assessment OR Advance Care Planning OR Advance Directives).sh.	
15.	9 AND 13	
16.	9 AND 14	
17.	or/15-16	2,176 articles retrieved

Table 3. Data extraction framework

Bibliometrics	Description	Coding
Study identification	First Author, year of publication	(journal's description)
Study characteristics	Study aim	(authors' description)
	Geographical location	Country
	Study setting	Inpatient, outpatient
	Type of study	Observational (i.e. qualitative, quantitative cross-sectional, quantitative longitudinal, mixed methods) or interventional study
Patient characteristics	Sample size	Number of patients
	Age	(years)
	Sex	(% females)
	Definition of multimorbidity	(authors' description)
	Prognosis or illness severity indices (if applicable)	e.g. less than 6 months of life or congestive heart failure NYHA II-IV
	Type of index condition (if applicable)	Cancer or non-malignant
Methods of data collection	Type of data collection	Interview, semi-structured interview, survey, focus

		group, questionnaire (authors' description)
	Context of the preference	Hypothetical / real preference-sensitive situation*
	Presentation of information on alternatives – Framing effect**	High-risk of positive-negative framing, low risk of framing or unclear
	Number of assessments	e.g. one assessment if cross- sectional, two or more assessments if longitudinal
	Time between assessments	If applicable
Phenomenon of interest	Description	Type of EoL preference queried e.g. cardiopulmonary resuscitation
	Results	e.g. percentage of participants for or against life-sustaining treatments (number of participants stating a preference out of all the patients included in the study)
Results / Conclusions		(authors' description)

EoL = End of Life; NYHA = New York Heart Association.

*Hypothetical preference-sensitive situation: EoL care preferences are measured by asking study participants to imagine themselves in a situation in the future that requires such care;

Real preference-sensitive situation: EoL care preferences are measured by asking study participants to state their preferences in a context that actually requires them to express a preference for such care. Examining preferences using hypothetical scenarios removes the acute stress of making decisions when confronted with an EoL situation.

**Framing effect: Cognitive bias caused by the influence of the way information is presented on the choices people make.

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	102-104
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	5-75
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	353-359
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input type="checkbox"/>	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	362-364
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	362-364
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	362-364
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	112-145
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	146-151

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	162-186 Table 1
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	187-192
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	195-197 Table 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	204-207
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	208-219
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	220-224
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	225-237 Table 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	235-237 Table 3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	242-247
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	248-258
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	248-258
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	259-265
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	248-258

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	259-261
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	242-247

NA = not applicable

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