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## Comparing the effectiveness and cost-effectiveness of self-management interventions in four high-priority chronic conditions in Europe (COMPAR-EU): a research protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034680
Article Type:	Protocol
Date Submitted by the Author:	01-Oct-2019
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Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Public health < INFECTIOUS DISEASES, QUALITATIVE RESEARCH, STATISTICS & RESEARCH METHODS, HEALTH ECONOMICS

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1 **Comparing the effectiveness and cost-effectiveness of self-management interventions**  
2 **in four high-priority chronic conditions in Europe (COMPAR-EU): a research protocol**

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Order review only

## 11 ABSTRACT

12 **Introduction:** Population ageing and increasing chronic illness burden has sparked  
13 interest in innovative care models. While self-management interventions (SMIs) are  
14 drawing increasing attention, evidence of their efficacy is mostly based on pairwise  
15 meta-analysis, generally derived from randomized controlled trials comparing  
16 interventions vs. a control or no intervention. As such, relevant efficacy data for  
17 comparisons among different SMIs that can be applied to specific chronic conditions is  
18 missing. Therefore, the contribution of the currently available evidence to aid decision-  
19 making at clinical, organisational, and policy levels is limited.

20 **Aim:** to identify, compare, and rank the most effective and cost-effective SMIs for adults  
21 with four high-priority chronic conditions: type 2 diabetes, obesity, chronic obstructive  
22 pulmonary disease, and heart failure.

23 **Methods and analysis:** All activities will be conducted as part of the COMPAR-EU  
24 Project, an EU-funded project designed to bridge the gap between current knowledge  
25 and practice on SMIs. In the first phase of the project, we will develop and validate a  
26 taxonomy, and a Core Outcome Set (COS) for each condition. These activities will inform  
27 a series of systematic review and network meta-analysis (NMA) about the effectiveness  
28 of SMIs. We will also perform a cost-effectiveness analysis of the most effective SMIs  
29 and an evaluation of contextual factors. We will finally develop tailored decision-making  
30 tools for the different relevant stakeholders.

31 **Ethics and dissemination:** Ethical approval was obtained from the local ethics  
32 committee (University Institute for Primary Care Research - IDIAP Jordi Gol). All patients  
33 and other stakeholders will provide informed consent prior to participation. This project  
34 has been funded by the EU Horizon 2020 research and innovation programme (grant  
35 agreement no. 754936). Results will be of interest to relevant stakeholder groups  
36 (patients, professionals, managers, policymakers and industry), and will be disseminated  
37 in a tailored multi-pronged approach that will include deployment of an interactive  
38 platform.

39 **Keywords:** Protocols & guidelines; Statistics & research methods; Qualitative research;  
40 Health economics; Public health.

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41 **ARTICLE SUMMARY**

42 **Strengths and limitations of this study:**

- 43 1. The project will result in the largest NMA of complex SMI interventions.
- 44 2. SMIs are inconsistently defined across the literature potentially generating a  
45 high level of heterogeneity for the NMA, which we will mitigate by developing  
46 a validated a taxonomy.
- 47 3. The development of COSs with input from patients and other stakeholders for  
48 each chronic condition will ensure that outcomes assessed in the NMA are  
49 relevant to the target users.
- 50 4. The comparative effectiveness analysis via NMA, cost-effectiveness, and  
51 contextual factors evaluation will provide new knowledge that should facilitate  
52 future implementation of successful SMIs.
- 53 5. An interactive platform will facilitate access to decision making tools relevant  
54 to the specific needs of the different target users.

## 55 INTRODUCTION

56 As population ageing accelerates worldwide, chronic illness will place an increasing  
57 burden on society and healthcare systems (1). Chronic conditions affect over 80% of  
58 people aged over 65 in Europe and account for an estimated 77% of disease burden, as  
59 measured by disability-adjusted life years (2). Furthermore, between 70% and 80% of  
60 healthcare costs in Europe can be attributed to chronic disease, and the current €700  
61 billion expenditure is expected to rise (3).

62 Self-management support has become a key strategy for addressing chronic disease  
63 burden (4), contributing to the paradigm shift from a paternalistic model where patients  
64 are viewed as passive recipients of care, towards more equitable and collaborative  
65 models of clinician-patient interaction (5).

66 COMPAR-EU is an EU-funded project designed to bridge the gap between current  
67 knowledge and practice on self-management interventions (SMIs). For the purpose of  
68 this project self-management is what individuals, families, and communities do to  
69 promote, maintain, or restore health and cope with illness and disability, with or without  
70 the support of health professionals, and including but not limited to self-prevention,  
71 self-diagnosis, self-medication, and coping with illness and disability (6).

72 Self-management of a chronic condition requires self-efficacy, largely understood as a  
73 person's confidence in their ability to cope with their illness (7). To be self-efficacious,  
74 people need special skills to cope with the consequences of the disease, including  
75 monitoring symptoms and clinical markers, understanding the implications of these, and  
76 adjusting behaviours treatment accordingly.

77 SMIs are supportive interventions systematically delivered or led by healthcare staff or  
78 other patients with the aim of building patients' confidence and equipping them with  
79 the necessary skills. Their purpose is to actively engage patients (and informal caregivers  
80 where appropriate) in the management of their disease (8). As such, they are more than  
81 merely didactic, instructional programmes, as their primary objective is to bring about  
82 changes in behaviour and trigger a sequence of positive knock-on effects (9).

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4 83 SMIs are complex interventions (9), typically characterised by multiple factors  
5 84 (components, formats, settings, target behaviours...) that interact over time as  
6 85 participants move back and forth between the intervention processes and everyday life,  
7 86 which can entail challenges in measuring effectiveness. Despite this, there is promising  
8 87 evidence that SMIs, under given conditions, can improve clinical outcomes in numerous  
9 88 chronic conditions, such as diabetes (reduction of haemoglobin A1c levels) (10), obesity  
10 89 (reduction of weight loss) (11,12), chronic obstructive pulmonary disease (COPD)  
11 90 (improvement of dyspnoea) (13), and heart failure (reduction of mortality) (14). SMIs  
12 91 have also been associated with improvements in patient-reported outcomes, such  
13 92 as quality of life, and more specific disease measures (15), such as self-efficacy (16)  
14 93 and adherence (17).

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25 94 Evidence on the efficacy of SMIs to date has mostly come from systematic reviews that  
26 95 have employed pairwise meta-analysis of RCTs. Systematic reviews pool evidence from  
27 96 RCTs comparing the same interventions and have long been considered as the highest  
28 97 standard in evidence-based health care. Pairwise meta-analysis, however, leaves a  
29 98 crucial gap, because it requires the RCT's that are pooled to have included the same  
30 99 interventions. To provide decision-makers, clinicians, and patients with solid evidence  
31 100 on how effective an SMI is for a given outcome and disease, multiple interventions need  
32 101 to be compared. In COMPAR-EU, we plan to do this by using NMA to assess the relative  
33 102 effectiveness of SMIs in four chronic conditions.

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42 103 NMA synthesises direct and indirect evidence across a network of multiple  
43 104 interventions. This method has numerous advantages: it provides more precise effect  
44 105 estimates, allows for the estimation of relative effectiveness between interventions that  
45 106 have not been compared directly, and provides a ranking of interventions by  
46 107 effectiveness, presenting thus a potential analytical advantage (18–22). NMA has been in  
47 108 use for some years, an empirical evaluation of 456 NMAs published up to 2015 showed that just  
48 109 16% of these addressed complex interventions (23) such as SMIs (24).

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56 110 While NMA allows us to compare different types of interventions within a health  
57 111 condition, it cannot aid in informing effectiveness across conditions. We know, for  
58 112 example, that certain SMIs, such as telemonitoring has positive effects on lipids levels

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4 113 for patients with diabetes (25), and on adherence for patients with heart failure(26) but  
5 114 the NMA can't answer which one of these interventions should be reimbursed from a  
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7 115 finite health care budget. Furthermore, a synthesis of trial data is by definition limited  
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9 116 to the duration of the trial, while often good estimates of long-term effects (such as  
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11 117 long-term weight loss) are needed for societal decision-making.

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14 118 To address these issues, we will develop simulation models in the four disease areas  
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16 119 which will translate benefits as identified by the NMA into long term health benefits  
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18 120 expressed in quality adjusted life years (QALYs), which enables us to compare not only  
19  
20 121 SMIs within the four conditions but also across them. The simulation models will also  
21  
22 122 include a cost-effectiveness component. Cost-effectiveness analyses are important as  
23  
24 123 they help to prioritise health expenditure. There is evidence that certain SMIs are cost-  
25  
26 124 effective. Weight reduction in obesity, for example, can produce short-term savings and  
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28 125 increase the chances of remaining in employment (27), resulting in additional societal  
29  
30 126 gains, while COPD management interventions can improve quality of life at generally  
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32 127 acceptable societal costs (28), and in some cases even result in short-term healthcare  
33  
34 128 cost savings (29). Secondary cardiovascular risk prevention programmes have the  
35  
36 129 potential to reduce direct healthcare expenditure and improve health outcomes (30).  
37  
38 130 While these results have not yet been structured into a consolidated body of knowledge,  
39  
40 131 they do indicate that investing in SMIs may be cost-effective.

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42 132 A better understanding of facilitators and barriers to successful programme  
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44 133 implementation is also essential. Contextual factors at various levels (patient, patient-  
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46 134 provider interaction, organisation and system) can all influence SMI uptake,  
47  
48 135 engagement, and success. Improving our understanding of how these factors influence  
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50 136 the effectiveness and cost-effectiveness of complex SMIs for chronic illness is much  
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52 137 needed.

#### 53 138 *Aim*

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55 139 COMPAR-EU is a multimethod interdisciplinary project that will run from 2018 to 2022.  
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57 140 The project has been designed to help bridge the gap between current knowledge and  
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59 141 practice in SMIs for chronic illness. Its aim is to identify, compare, and rank the most  
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4 142 effective SMIs for adults living with four high-priority chronic conditions (type 2  
5 143 diabetes, obesity, COPD, and heart failure), and among these interventions, categorise  
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7 144 the most cost-effective and feasible SMIs. The results of the project will facilitate  
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9 145 informed decision-making and support the implementation of best practices in different  
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11 146 healthcare contexts through an interactive platform featuring decision-making tools,  
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13 147 and other end products adapted to the needs of a range of end users, such as  
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15 148 policymakers, guideline developers, researchers, healthcare professionals, patients, and  
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17 149 industry.

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19 150 The specific objectives are to: 1) validate a taxonomy of SMIs; 2) identify and prioritise  
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21 151 SMI outcomes from the perspective of both patients and practitioners, culminating in a  
22  
23 152 Core Outcome Set (COS) for each condition; 3) carrying out systematic reviews to  
24  
25 153 synthesise existing evidence on SMIs from RCTs; 4) compare the relative effectiveness  
26  
27 154 of SMIs through NMA; 5) model the cost-effectiveness impact of SMIs; 6) analyse  
28  
29 155 contextual and implementation factors, and; 7) develop and pilot decision-making tools  
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31 156 to facilitate access to and use of the most effective SMIs among key target end users.

## 32 33 157 **METHODS AND ANALYSIS**

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36 158 The COMPAR-EU project is divided into seven phases following to our specific objectives.  
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38 159 Each phase is further described below and in Figure 1 (COMPAR-EU Phases and main  
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41 160 tasks)

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44 161 *(Figure 1. COMPAR-EU Phases and main tasks)*

### 45 46 47 162 **Phase 1: Refinement and validation of a taxonomy of SMIs**

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49 163 Taxonomies are formal systems for classifying multifaceted, complex phenomena  
50  
51 164 according to a set of common conceptual domains and dimensions; their use increases  
52  
53 165 clarity in defining and comparing complex phenomena (31). Several taxonomies for SMIs  
54  
55 166 have been employed in the literature, but so far have focused in a specific area of the  
56  
57 167 intervention (e.g. self-management behaviour) and haven't been validated. In the first  
58  
59 168 phase of COMPAR-EU, we will produce a conceptual map and classification system that  
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169 will be evaluated by self-management experts and stakeholders (including patients)

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4 170 through a modified Delphi technique consisting of a two-rounds online survey. The  
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6 171 resulting feedback and suggestions for refinement will be integrated into a new version  
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8 172 of a self-management taxonomy to be tested by the research team when classifying the  
9  
10 173 SMIs reported in the analysed RCTs.

## 11 174 **Phase 2: Develop Core Outcome Sets for SMIs addressing the four conditions**

12  
13 175 Interventions can only be compared across studies when they share at least some  
14  
15 176 common outcomes, and appropriate selection of outcomes is essential if research is to  
16  
17 177 guide decision-making and inform policy. We will therefore develop a COS for each of  
18  
19 178 the four chronic conditions included in the project.

### 20 179 • *Outcome catalogue*

21  
22 180 The first step is to create an exhaustive database listing outcomes reported in previous  
23  
24 181 EU projects (PRO-STEP (32), and EMPATHIE (33)) and COMET, a COS database and other  
25  
26 182 relevant organisations (using a snowballing technique). For each condition, outcomes  
27  
28 183 will be classified into different categories, such as clinical outcomes, patient-reported  
29  
30 184 outcome measures, or resource utilisation.

### 31 185 • *Systematic review of how patients value self-management outcomes*

32  
33 186 To identify patient priorities for self-management in the selected conditions we will  
34  
35 187 conduct a scoping review and a series of specific overviews for each condition about  
36  
37 188 what patients, and their caregivers value on SMIs.

### 38 39 40 189 • *Delphi survey with patient representatives*

41  
42 190 To help prioritise the outcomes identified, we will use a modified Delphi survey  
43  
44 191 administered to a convenience sample of patients, carers, and patient representatives  
45  
46 192 to ensure that our research addresses outcomes that matter to patients (and other  
47  
48 193 stakeholders). Although patient participation in outcome selection has been studied  
49  
50 194 very little, it has been described as a good practice to minimise the influence of power  
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52 195 differentials between stakeholders (34). Four panels of patients and carers, for each  
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54 196 disease separately (5-8 members) will be given the task of prioritising relevant outcomes  
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56 197 on a Likert scale.

### 57 198 • *Final consensus workshop*

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4 199 The proposals for each of the four COSs will be presented to a panel of patients and other  
5 200 stakeholders (healthcare professionals, policymakers and researchers) in a workshop that aims to  
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7 201 achieve consensus across groups on the most important outcomes to include in the COS.  
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9 202 Participants will be previously provided with the results of the patient prioritization process, and  
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11 203 with the results of the synthesis of results from the literature review. We will establish criteria to  
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13 204 address potential discrepancies across stakeholders.

14 205 **Phase 3: Systematic review – Descriptive synthesis of the evidence**

16 206 • *Preparations for data collection*

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18 207 We will develop a protocol following Cochrane guidance (35,36) and hold training  
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20 208 sessions for those responsible for collecting data. Before the extraction process, all  
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22 209 reviewers will be trained and undergo calibration to ensure inter-rater agreement.  
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24 210 Additional, in the extraction process all data collected will be reviewed by an  
25  
26 211 independent researcher to ensure quality.

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28 212 • *Literature search and screening*

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30 213 To identify relevant RCTs, we will draw on the databases of previous European projects  
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32 214 (PRO-STEP, and EMPATHIE) that have identified hundreds of systematic reviews on SMIs  
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34 215 for diabetes, obesity, COPD, and heart failure. We will then update existing data through  
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36 216 new searches in MEDLINE, CINAHL, Embase, Cochrane, and PsycINFO. We will include  
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38 217 RCTs that compare SMIs in adults with at least one of our conditions of interest (type 2  
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40 218 diabetes, obesity, COPD, or heart failure) and are published in English or Spanish.

41 219 • *Data extraction and collection*

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43 220 An estimated 4,000 RCTs, based on the results of a previous overview (32), will be  
44  
45 221 studied to extract relevant data on SMI in the four prioritized chronic conditions. These  
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47 222 data include among others, patient characteristics, disease characteristics and  
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49 223 comorbidities, intervention characteristics (guided by the taxonomy), outcomes (guided  
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51 224 by the four COSs), results, and information on study design and risk of bias. Specific  
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53 225 attention will be paid to subgroups of patients according to comorbidity, gender, and  
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55 226 socioeconomic variables (e.g. health literacy).

56 227 • *Descriptive analysis and summary of SMIs and outcomes*

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4 228 SMIs and outcomes identified in the RCTs will be described and summarised to provide  
5 229 information on type and number of interventions, outcome results, patient  
6 230 characteristics, and presence of comorbidities for each of the four conditions.  
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9 231 **Phase 4: Systematic review: NMA and certainty of evidence**

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12 232 • *Network meta-analysis*

13 233 We will initially develop theoretical models that make explicit the mechanisms through  
14 234 which the different SMIs operate on a given outcome. Based on our taxonomy of  
15 235 interventions, these models will identify hierarchies of elements (type of support  
16 236 provided, expected self-management behaviour, mode of delivery of the intervention,  
17 237 provider, etc.) that operate on the outcome to identify which components or which  
18 238 combinations of components are most effective.

19 239 Additionally to the standard NMA models, we will employ component NMA (37–39) to  
20 240 identify key intervention components and create a ranking of SMIs according to their  
21 241 effectiveness. During this process, it is crucial that major assumptions of NMA like  
22 242 transitivity (that there must be no relevant discrepancy or inconsistency between direct  
23 243 and indirect evidence(40)) are satisfied, as the validity of results will depend on the  
24 244 plausibility of the assumptions made. We will also explore the distribution of effect  
25 245 modifiers (e.g., comorbidities, gender, and socioeconomic factors) across the various  
26 246 comparisons. This will include differentiation, if possible, between the various forms of  
27 247 ‘usual care’ reported in the included studies.

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30 248 • *Evaluation and summary of the certainty of the evidence*

31 249 To guide users in knowing how much confidence they can place in the summarised  
32 250 evidence; we will rate the certainty of evidence, obtained through the network meta-  
33 251 analysis, for each outcome of interest, using the Grading of Recommendations,  
34 252 Assessment, Development and Evaluations (GRADE) approach(41–43). Additionally, we  
35 253 will apply an alternative approach, the CInEMA framework, to assess the confidence in  
36 254 the results by exploring how information flows in the network and how much studies at  
37 255 high/unclear risk of bias affect the network meta-analysis estimates. We will explore  
38 256 how the assessment differs between these two approaches.  
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59 258 **Phase 5: Model the Cost-effectiveness of effective SMIs**  
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4 259 For the cost-effectiveness analysis, data on short term effects on intermediate  
5 260 outcomes (e.g. BMI, HbA1C) from the NMA will serve as input for simulation models  
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7 261 that extrapolate these effects into long term health effects expressed in Quality  
8  
9 262 Adjusted Life Years (QALYs). These health benefits will be combined with  
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11 263 cost prediction to estimate the incremental cost per quality-adjusted life  
12  
13 264 year gained. To develop simulation models in the four chronic conditions the first step  
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15 265 will be to develop a conceptual model informed by a review of  
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17 266 the literature (44). Decisions will also be taken at this stage on which statistical  
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19 267 techniques and models to use (e.g., discrete-event models, Markov models, patient  
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21 268 level simulation models). These decisions will be guided by good practice guidelines  
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23 269 from pharmacoeconomic communities of medical decision making and the  
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25 270 International Society for Pharmacoeconomics and Outcomes Research (45) and  
26  
27 271 available data. In all four disease models, the natural course of each of the four  
28  
29 272 study conditions will be modelled with incorporation of background events and  
30  
31 273 disease-specific mortality and morbidity. Intervention costs will take into account  
32  
33 274 societal, healthcare, and patient perspectives, and where possible, special attention will  
34  
35 275 be given to societal costs that have historically been understudied (e.g., productivity  
36  
37 276 gains and changes in caregiver burden and costs in life-years gained (39). By expressing  
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39 277 health benefits in QALYs we will be able to produce a ranking of the most cost-  
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41 278 effective SMI under, within and across conditions.

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279 **Phase 6: Analyse the contextual factors that promote implementation in real life**  
280 **contexts**

281 For each of the most effective SMIs identified for the four chronic conditions we will  
282 perform a realist systematic review (44) to identify key determinants of success (or  
283 failure), such as intervention settings (e.g., whether on a primary care level or hospital  
284 level care) and mechanisms (e.g., engagement processes) that produce specific  
285 outcomes. At the patient level, special attention will be paid to comorbidities, gender,  
286 and socioeconomic dimensions such as health literacy to better understand how these  
287 influence the implementation of the selected SMIs. We will then use a modified Delphi  
288 method to establish the importance of these contextual factors in the target countries  
289 (Belgium, Germany, Greece, the Netherlands & Spain,).

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4 290 **Phase 7: Development and piloting of the COMPAR-EU information technology platform, and**  
5 291 **preparation for future implementation**  
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8 292 We will develop a technological platform that will integrate all the information and  
9  
10 293 evidence synthesised during the different phases of the project to facilitate decision  
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12 294 making for target end users (patients, healthcare professionals, policymakers,  
13  
14 295 researchers, and small and medium-sized enterprises (SMEs)). The platform will include  
15 296 the following GRADE-based tools:

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17 297 - Evidence profiles and Interactive Summary of Findings (SoF) tables(45): these  
18  
19 298 presentation will provide information in different formats about the quality of  
20  
21 299 evidence, and magnitude of relative and absolute effects for each of the core  
22  
23 300 outcomes identified.
- 24 301 - Evidence to Decision frameworks (EtD): using semi-automatic templates,  
25  
26 302 interactive EtD frameworks (46) will be completed for a number of priority  
27  
28 303 questions that will take into account the magnitude of desirable and undesirable  
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30 304 effects, stakeholder views on the importance of different outcomes, information  
31  
32 305 on resource use and cost-effectiveness, impact on equity, and other aspects like  
33  
34 306 acceptability or feasibility of the interventions. The frameworks will include draft  
35  
36 307 recommendations that could be then applied or adapted to different settings.
- 37 308 - Patient decision aids: will be developed in plain-language for all selected situations  
38  
39 309 identified in the previous phases of the study. The aids will be produced in six  
40  
41 310 languages (English, French, German, Spanish, Dutch, and Greek) and will include  
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43 311 information obtained in some of the phases included in the project.

44 312 • *Development of COMPAR-EU online platform*  
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46 313 The COMPAR-EU online platform will feature structured interfaces tailored to the needs  
47  
48 314 of different end users. It will offer access to the evidence (including taxonomy of  
49  
50 315 interventions and COSs) and decision-making tools generated during the project and will  
51  
52 316 be designed such that after answering a few simple questions, users will be guided to  
53  
54 317 the tool or product that best suits their needs (Figure 2 illustrates the main products to  
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56 318 be integrated into the platform and expected end-users).  
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320 *Figure 2. COMPAR-EU Platform, decision-making tools and other end products*

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- *Piloting and refinement of decision-making tools with different stakeholders*

323 The COMPAR-EU platform will be piloted with end users and relevant stakeholders to  
324 gauge potential barriers and understand how to position the decision-making tools in  
325 the target healthcare markets. A series of small-scale tests will be used to pilot the  
326 decision aids among patients, health professionals, and EtDs and other products with  
327 other stakeholders who may be involved in implementing the tools in the five  
328 participating countries (e.g., policymakers, industry, and representatives of patient  
329 associations). We will organise focus groups and user experience tests in simulated  
330 settings using techniques such as thinking-out-loud to gain input for further optimisation  
331 of the tools and feedback on the opportunities for implementation in the participating  
332 countries and settings.

333 A group of at least 60 end-users (policymakers, guidelines developers, and researchers  
334 depending on the type of tools) will pilot-test the COMPAR-EU electronic decision-  
335 making tools. End-users will be invited to test the tools and give feedback via semi-  
336 structured online interviews. The tools will be piloted in different scenarios and  
337 countries to identify facilitators and barriers to implementation. Results of the piloting  
338 will be used to further improve the tools.

339 

- *Preparation of future implementation*

340 Even with well-developed and user-friendly decision-tools, integration in existing policy  
341 and regulatory frameworks is crucial for successful uptake of our recommendations. We  
342 will conduct a systematic search of the scientific and grey literature to identify and  
343 analyse the multiple policy and regulatory frameworks that could influence the uptake  
344 of the self-management and decision-making tools designed within COMPAR-EU. We  
345 will also hold workshops with industry, pharma, and SMEs to identify business  
346 opportunities resulting from the research findings that could result in long-term  
347 sustainable dissemination.

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3 348 **PATIENT AND PUBLIC INVOLVEMENT**  
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6 349 Patients are a key component of the COMPAR-EU project from start to finish and their  
7  
8 350 interests are represented by the European Patient Forum (EPF), which is one of the  
9  
10 351 consortium partners. Together with other stakeholders, they will be involved in different  
11  
12 352 aspects of the project including prioritisation of core outcomes and testing of interactive  
13  
14 353 tools. A core group of partners, led by the EPF, will also be created to ensure co-  
15  
16 354 production and establishment of explicit criteria to incorporate patient views into  
17  
18 355 project outcomes, products, and communication interventions. Plain-language material  
19  
20 356 will also be developed to support the main end products of the project.

21  
22 357 **ETHICS AND DISSEMINATION**  
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24

25 358 The project coordinator's (Avedis Donabedian Research Institute) requested the overall  
26  
27 359 ethical approval for the project to our local Clinical Research Ethics Committee (CEIC)  
28  
29 360 (the University Institute for Primary Care Research - IDIAP Jordi Gol). Ethical approval  
30  
31 361 was granted on March 2018. Results are of interest to several stakeholder groups  
32  
33 362 (patients, professionals, managers, policymakers and industry) and will be disseminated  
34  
35 363 in a tailored multi-pronged approach, including the creation of an interactive platform.  
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37 364 The data generated by the project will be managed following the Golden Open access  
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39 365 as defined by the European Commission for Horizon 2020 research projects (47).  
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366 **LIST OF ABBREVIATIONS**

367 COS – Core Outcome Sets

368 EPF – European Patient Forum

369 NMA – Network meta-analysis

370 SMIs – Self-management interventions

371 RCT – Randomised Control Trial

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For peer review only

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3 **373 DECLARATIONS**  
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6 **374 PATIENT AND PUBLIC INVOLVEMENT**  
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8

9 375 European Patients Forum (EPF) a key umbrella organization in patient representation  
10  
11 376 and European level is a partner of this project and as such has contributed to the project  
12  
13 377 from its inception and design.  
14

15  
16 378 Furthermore we have planned for patient participation in key stages of the project,  
17  
18 379 including the selection of outcomes for the Core Outcome Sets, advise towards patient  
19  
20 380 end products and participating in the design and piloting of the COMPAR-EU platform  
21  
22 381 and related decision making tools.  
23

24  
25 382  
26

27 **383 AUTHORS' CONTRIBUTIONS**  
28

29  
30 384 • Marta Ballester contributed to the design of the project and prepared the  
31  
32 385 manuscript of the paper.  
33

34 386 • Carola Orrego contributed to the design of the project and reviewed and  
35  
36 387 contributed to the manuscript of the paper.  
37

38 388 • Monique Heymans contributed to the design of the project and reviewed and  
39  
40 389 contributed to the manuscript of the paper.  
41

42 390 • Pablo Alonso-Coello contributed to the design of the project and reviewed and  
43  
44 391 contributed to the manuscript of the paper.  
45

46 392 • Matthijs Versteegh contributed to the design of the project and reviewed and  
47  
48 393 contributed to the manuscript of the paper.  
49

50 394 • Dimitris Mavridis contributed to the design of the project and reviewed and  
51  
52 395 contributed to the manuscript of the paper.  
53

54 396 • Oliver Groene contributed to the design of the project and reviewed and  
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56 397 contributed to the manuscript of the paper.  
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- 398 • Kaisa Immonen contributed to the design of the project and reviewed and  
399 contributed to the manuscript of the paper.
- 400 • Cordula Wagner contributed to the design of the project and reviewed and  
401 contributed to the manuscript of the paper.
- 402 • Carlos Canelo contributed to the design of the project and reviewed and  
403 contributed to the manuscript of the paper.
- 404 • Rosa Suñol contributed to the design of the project and reviewed and  
405 contributed to the manuscript of the paper.
- 406
- 407
- 408 • Acknowledgments As well, we would like to express our gratitude to Ana Isabel  
409 González, Aretj-Angeliki Veroniki, Claudia Valli, Claudio Alfonso Rocha Calderón,  
410 Ena Niño de Guzmán, Estela Camus, Giorgos Seitidis, Hector Pardo-Hernandez ,  
411 Jany Rademakers, Jessica Beltrán, Karla Salas, Kevin Pacheco-Barrios, Lyudmil  
412 Ninov, Maria Petropoulou, Marieke van der Gaag, Montserrat León, Nina Adrion,  
413 Rune Poortvliet, Stella Zevgiti, Valentina Strammiello for their valuable  
414 assistance in conducting this proposal.
- 415 • Funding: This work was supported by European Union’s Horizon 2020 research  
416 and innovation programme under grant agreement No 754936
- 417 • Competing interest statement: no competing interests.

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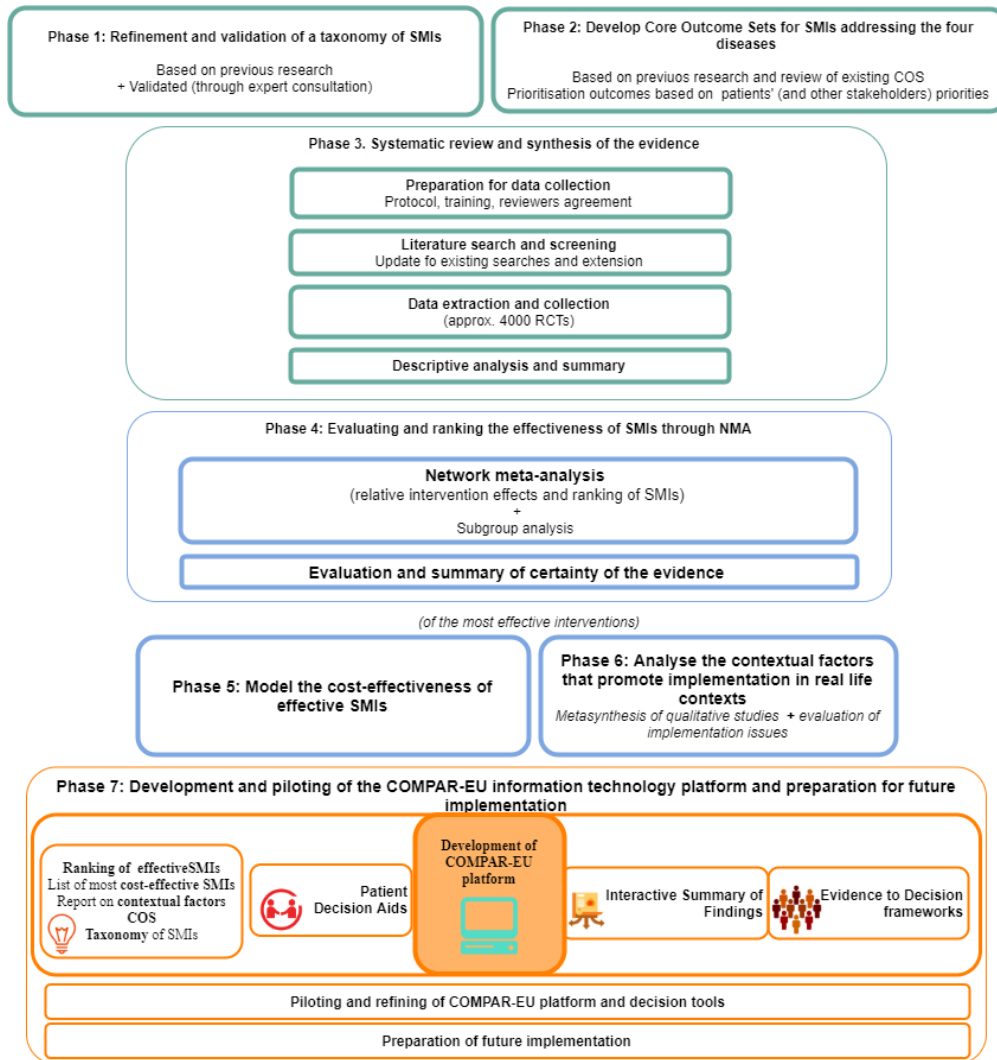
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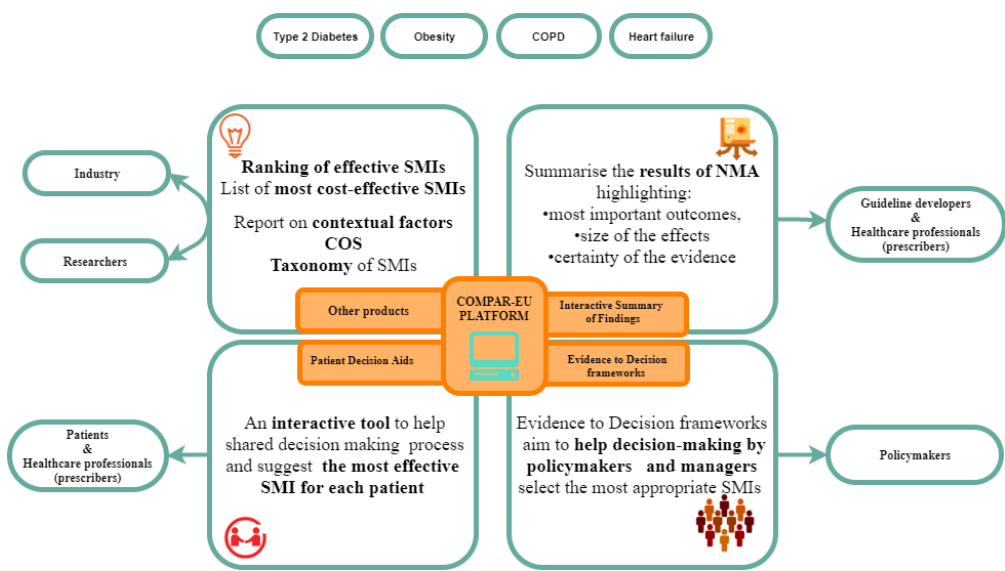
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COMPAR-EU Main tasks

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COMPAR-EU online platform and relation to target end-users

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# BMJ Open

## Comparing the effectiveness and cost-effectiveness of self-management interventions in four high-priority chronic conditions in Europe (COMPAR-EU): a research protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034680.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Dec-2019
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<b>Primary Subject Heading</b>:	Research methods
Secondary Subject Heading:	Evidence based practice, Global health, Health economics, Health policy
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Public health < INFECTIOUS DISEASES, QUALITATIVE RESEARCH, STATISTICS & RESEARCH METHODS, HEALTH ECONOMICS

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5 1 **Comparing the effectiveness and cost-effectiveness of self-management**  
6 2 **interventions in four high-priority chronic conditions in Europe (COMPAR-EU): a**  
7 3 **research protocol**  
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## 13 ABSTRACT

14 **Introduction:** Population ageing and increasing chronic illness burden has sparked  
15 interest in innovative care models. While self-management interventions (SMIs) are  
16 drawing increasing attention, evidence of their efficacy is mostly based on pairwise  
17 meta-analysis, generally derived from randomized controlled trials comparing  
18 interventions vs. a control or no intervention. As such, relevant efficacy data for  
19 comparisons among different SMIs that can be applied to specific chronic conditions is  
20 missing. Therefore, the relevance of the available evidence for decision-making at  
21 clinical, organisational, and policy levels is limited.

22 **Aim:** to identify, compare, and rank the most effective and cost-effective SMIs for  
23 adults with four high-priority chronic conditions: type 2 diabetes, obesity, chronic  
24 obstructive pulmonary disease, and heart failure.

25 **Methods and analysis:** All activities will be conducted as part of the COMPAR-EU  
26 Project, an EU-funded project designed to bridge the gap between current knowledge  
27 and practice on SMIs. In the first phase of the project, we will develop and validate a  
28 taxonomy, and a Core Outcome Set (COS) for each condition. These activities will  
29 inform a series of systematic review and network meta-analysis (NMA) about the  
30 effectiveness of SMIs. We will also perform a cost-effectiveness analysis of the most  
31 effective SMIs and an evaluation of contextual factors. We will finally develop tailored  
32 decision-making tools for the different relevant stakeholders.

33 **Ethics and dissemination:** Ethical approval was obtained from the local ethics  
34 committee (University Institute for Primary Care Research - IDIAP Jordi Gol). All  
35 patients and other stakeholders will provide informed consent prior to participation.  
36 This project has been funded by the EU Horizon 2020 research and innovation  
37 programme (grant agreement no. 754936). Results will be of interest to relevant  
38 stakeholder groups (patients, professionals, managers, policymakers and industry),  
39 and will be disseminated in a tailored multi-pronged approach that will include  
40 deployment of an interactive platform.

41 **Keywords:** Protocols & guidelines; Statistics & research methods; Qualitative research;  
42 Health economics; Public health.

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## 43 ARTICLE SUMMARY

### 44 Strengths and limitations of this study:

- 45 1. The project will result in the largest NMA of complex SMI interventions.
- 46 2. SMIs are inconsistently defined across the literature potentially generating a  
47 high level of heterogeneity for the NMA, which we will mitigate by developing  
48 a validated taxonomy.
- 49 3. The development of COSs with input from patients and other stakeholders for  
50 each chronic condition will ensure that outcomes assessed in the NMA are  
51 relevant to the target users.
- 52 4. The comparative effectiveness analysis via NMA, cost-effectiveness, and  
53 contextual factors evaluation will provide new knowledge that should  
54 facilitate future implementation of successful SMIs.
- 55 5. An interactive platform will facilitate access to decision making tools relevant  
56 to the specific needs of the different target users.



## 57 INTRODUCTION

58 As population ageing accelerates worldwide, chronic illness will place an increasing  
59 burden on society and healthcare systems (1). Chronic conditions affect over 80% of  
60 people aged over 65 in Europe and account for an estimated 77% of disease burden, as  
61 measured by disability-adjusted life years (2). Furthermore, between 70% and 80% of  
62 healthcare costs in Europe can be attributed to chronic disease, and the current €700  
63 billion expenditure is expected to rise (3).

64 Self-management support has become a key strategy for addressing chronic disease  
65 burden (4), contributing to the paradigm shift from a paternalistic model where  
66 patients are viewed as passive recipients of care, towards more equitable and  
67 collaborative models of clinician-patient interaction (5).

68 COMPAR-EU is an EU-funded project designed to bridge the gap between current  
69 knowledge and practice on self-management interventions (SMIs). For the purpose of  
70 this project we define self- management as “actions that individuals, families, and  
71 communities engage in to promote, maintain, or restore health and cope with illness  
72 and disability, with or without the support of health professionals, and including but  
73 not limited to self-prevention, self-diagnosis, self-medication, and coping with illness  
74 and disability” (6).

75 Self-management of a chronic condition requires self-efficacy, largely understood as a  
76 person’s confidence in their ability to cope with their illness (7). To be self-efficacious,  
77 people need special skills to cope with the consequences of the disease, including  
78 monitoring symptoms and clinical markers, understanding the implications of these,  
79 and adjusting behaviours treatment accordingly.

80 SMIs are supportive interventions systematically delivered or led by healthcare staff or  
81 other patients with the aim of building patients’ confidence and equipping them with  
82 the necessary skills. Their purpose is to actively engage patients (and informal  
83 caregivers where appropriate) in the management of their disease (8). As such, they  
84 are more than merely didactic, instructional programmes, as their primary objective is

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4 85 to bring about changes in behaviour and trigger a sequence of positive knock-on  
5 86 effects (9).  
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8 87 SMIs are complex interventions (9), typically characterised by multiple factors  
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10 88 (components, formats, settings, target behaviours...) that interact over time as  
11  
12 89 participants move back and forth between the intervention processes and everyday  
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14 90 life, which can entail challenges in measuring effectiveness. Despite this, there is  
15  
16 91 promising evidence that SMIs, under given conditions, can improve clinical outcomes in  
17  
18 92 numerous chronic conditions, such as diabetes (reduction of haemoglobin A1c levels)  
19  
20 93 (10), obesity (reduction of weight loss) (11,12), chronic obstructive pulmonary disease  
21  
22 94 (COPD) (improvement of dyspnoea) (13), and heart failure (reduction of  
23  
24 95 mortality) (14). SMIs have also been associated with improvements in patient-  
25  
26 96 reported outcomes, such as quality of life, and more specific disease measures  
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28 97 (15), such as self-efficacy (16) and adherence (17).  
29

30 98 Evidence on the efficacy of SMIs to date has mostly come from systematic reviews that  
31  
32 99 have employed pairwise meta-analysis of RCTs. Systematic reviews pool evidence from  
33  
34 100 RCTs comparing the same interventions and have long been considered as the highest  
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36 101 standard in evidence-based health care. Pairwise meta-analysis, however, leaves a  
37  
38 102 crucial gap, because it requires the RCT's that are pooled to have included the same  
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40 103 interventions. To provide decision-makers, clinicians, and patients with solid evidence  
41  
42 104 on how effective an SMI is for a given outcome and disease, multiple interventions  
43  
44 105 need to be compared. In COMPAR-EU, we plan to do this by using NMA to assess the  
45  
46 106 relative effectiveness of SMIs in four chronic conditions.  
47

48 107 NMA synthesises direct and indirect evidence across a network of multiple  
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50 108 interventions. This method has numerous advantages: it provides more precise effect  
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52 109 estimates, allows for the estimation of relative effectiveness between interventions  
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54 110 that have not been compared directly, and provides a ranking of interventions by  
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56 111 effectiveness, presenting thus a potential analytical advantage (18–22). NMA has been  
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58 112 in use for some years, an empirical evaluation of 456 NMAs published up to 2015  
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60 113 showed that just 16% of these addressed complex interventions (23) such as SMIs (24).

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4 114 To support future reimbursement decisions based on estimates of the long-term  
5 115 effects of SMIs, we will develop simulation models in the four disease areas which will  
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7 116 translate benefits as identified by the NMA into long term health benefits expressed in  
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9 117 quality adjusted life years (QALYs), which enables us to compare not only SMIs within  
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11 118 but also across the four conditions. The simulation models will also include a cost-  
12  
13 119 effectiveness component. Cost-effectiveness analyses are important as they help to  
14  
15 120 prioritise health expenditure. There is evidence that certain SMIs are cost-effective.  
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17 121 Weight reduction in obesity, for example, can produce short-term savings and increase  
18  
19 122 the chances of remaining in employment (25), resulting in additional societal gains,  
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21 123 while COPD management interventions can improve quality of life at generally  
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23 124 acceptable societal costs (26), and in some cases even result in short-term healthcare  
24  
25 125 cost savings (27). Secondary cardiovascular risk prevention programmes have the  
26  
27 126 potential to reduce direct healthcare expenditure and improve health outcomes (28).  
28  
29 127 While these results have not yet been structured into a consolidated body of  
30  
31 128 knowledge, they do indicate that investing in SMIs may be cost-effective.

32  
33 129 A better understanding of facilitators and barriers to successful programme  
34  
35 130 implementation is also essential. Contextual factors at various levels (patient, patient-  
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37 131 provider interaction, organisation and system) can all influence SMI uptake,  
38  
39 132 engagement, and success. Improving our understanding of how these factors influence  
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41 133 the effectiveness and cost-effectiveness of complex SMIs for chronic illness is much  
42  
43 134 needed.

#### 44 135 *Aim*

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46 136 COMPAR-EU is a multimethod interdisciplinary project that will run from 2018 to 2022.  
47  
48 137 The project has been designed to help bridge the gap between current knowledge and  
49  
50 138 practice in SMIs for chronic illness. Its aim is to identify, compare, and rank the most  
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52 139 effective SMIs for adults living with four high-priority chronic conditions (type 2  
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54 140 diabetes, obesity, COPD, and heart failure), and among these interventions, categorise  
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56 141 the most cost-effective and feasible SMIs. The results of the project will facilitate  
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58 142 informed decision-making and support the implementation of best practices in  
59  
60 143 different healthcare contexts through an interactive platform featuring decision-

144 making tools, and other end products for policymakers, guideline developers,  
145 researchers, healthcare professionals, patients, and industry.

146 The specific objectives are to: 1) validate a taxonomy of SMIs; 2) identify and prioritise  
147 SMI outcomes from the perspective of both patients and practitioners, culminating in a  
148 Core Outcome Set (COS) for each condition; 3) carrying out systematic reviews to  
149 synthesise existing evidence on SMIs from RCTs; 4) compare the relative effectiveness  
150 of SMIs through NMA; 5) model the cost-effectiveness impact of SMIs; 6) analyse  
151 contextual and implementation factors, and; 7) develop and pilot decision-making  
152 tools to facilitate access to and use of the most effective SMIs among key target end  
153 users.

## 154 **METHODS AND ANALYSIS**

155 The COMPAR-EU project is divided into seven phases following to our specific  
156 objectives. Each phase is further described below and in Figure 1 (COMPAR-EU Phases  
157 and main tasks)

158 *(Figure 1. COMPAR-EU Phases and main tasks)*

### 159 **Phase 1: Refinement and validation of a taxonomy of SMIs**

160 Taxonomies are formal systems for classifying multifaceted, complex phenomena  
161 according to a set of common conceptual domains and dimensions; their use increases  
162 clarity in defining and comparing complex phenomena (29). Several taxonomies for  
163 SMIs have been developed in the literature, but so far have focused in a specific area  
164 of the intervention (e.g. self-management behaviour) and haven't been validated. In  
165 the first phase of COMPAR-EU, we will produce a conceptual map and classification  
166 system that will be evaluated by self-management experts and stakeholders (including  
167 patients) through a modified Delphi technique consisting of a two-rounds online  
168 survey. The list of candidate participants will include authors on self-management or  
169 related topics taxonomies, professional experts in self-management and patient  
170 representatives. The resulting feedback and suggestions for refinement will be

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4 171 integrated into a new version that will be tested by the research team when classifying  
5 172 the SMIs reported in the RCTs that will be included in the NMA.

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7 173 **Phase 2: Development of Core Outcome Sets for each condition**

8  
9 174 Interventions can only be compared across studies when they share at least some  
10  
11 175 common outcomes, and appropriate selection of outcomes is essential if research is to  
12  
13 176 guide decision-making and inform policy. We will therefore develop a COS for each of  
14  
15 177 the four chronic conditions included in the project.

16 178 • *Outcome catalogue*

17  
18 179 The first step is to create an exhaustive database listing outcomes reported in previous  
19  
20 180 EU projects (PRO-STEP (30), and EMPATHIE (31)) and COMET, a COS database and  
21  
22 181 other relevant organisations (using a snowballing technique). For each condition,  
23  
24 182 outcomes will be classified into different categories, such as clinical outcomes, patient-  
25  
26 183 reported outcome measures, or resource utilisation.

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28 184 • *Systematic review of how patients value self-management outcomes*

29  
30 185 To identify patient priorities for self-management in the selected conditions we will  
31  
32 186 conduct a scoping review, of quantitative and qualitative studies, and a series of  
33  
34 187 specific overviews for each condition about what patients, and their caregivers' value  
35  
36 188 on SMIs.

37  
38 189 • *Delphi survey with patient representatives*

39  
40 190 We plan to include patient participation in our outcome selection as it has been  
41  
42 191 described as a good practice to minimise the influence of power differentials between  
43  
44 192 stakeholders (32). We will use a modified Delphi survey administered to a  
45  
46 193 convenience sample of patients, and patient representatives to ensure that our  
47  
48 194 research addresses outcomes that matter to patients (and other stakeholders). Four  
49  
50 195 panels of patients and carers, for each disease separately (5-8 members) will be given  
51  
52 196 the task of prioritising relevant outcomes on a Likert scale.

53 197 • *Consensus workshop*

54  
55 198 The proposals for each of the four COSs will be presented to a panel of patients and other  
56  
57 199 stakeholders (healthcare professionals, policymakers and researchers) in a workshop that aims  
58  
59 200 to achieve consensus across groups on the most important outcomes to include in each COS.

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4 201 Participants will be previously provided with the results of the patient prioritization process, and  
5 202 with the results of the synthesis of results from the literature review. We will establish criteria to  
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7 203 address potential discrepancies across stakeholders.  
8

9 204 **Phase 3: Systematic review – Descriptive synthesis of the evidence**

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11 205 • *Preparations for data collection*

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13 206 We will develop a protocol following Cochrane guidance (33,34) and hold training  
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15 207 sessions for those responsible for collecting data. Before the extraction process, all  
16  
17 208 reviewers will be trained and undergo calibration to ensure inter-rater agreement.  
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19 209 Additional, in the extraction process all data collected will be reviewed by an  
20  
21 210 independent researcher to ensure quality.

22 211 • *Literature search and screening*

23  
24 212 To identify relevant RCTs, we will draw on the databases of previous European project  
25  
26 213 (PRO-STEP) that identified hundreds of systematic reviews on SMIs for diabetes,  
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28 214 obesity, COPD, and heart failure. We will use these RCTs published from 2000 up to  
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30 215 2015 (last date of SR publication included in those projects) in our project, and update  
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32 216 this data set through new searches in MEDLINE, CINAHL, Embase, Cochrane, and  
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34 217 PsycINFO. We will include RCTs that compared SMIs in adults with at least one of our  
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36 218 conditions of interest (type 2 diabetes, obesity, COPD, or heart failure) and are  
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38 219 published in English or Spanish. The search will be focused in RCTs published from  
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40 220 2015 to 2018 to complement the findings of the SR included in PRO-STEP, with the  
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42 221 possibility of including previous years if the systematic reviews from PRO-STEP haven't  
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44 222 covered those previous years sufficiently. An total estimate of 4,000 RCTs, based on  
45  
46 223 the results of a previous overview (30), will be included for the four prioritized chronic  
47  
48 224 conditions.

49 225 • *Data extraction and collection*

50 226 We will extract data including: patient characteristics, disease characteristics and  
51  
52 227 comorbidities, intervention characteristics (guided by the taxonomy), outcomes  
53  
54 228 (guided by the four COSs), results, and information on study design and risk of bias.  
55  
56 229 Specific attention will be paid to subgroups of patients according to comorbidity,  
57  
58 230 gender, and socioeconomic variables (e.g. health literacy).

59 231 • *Descriptive analysis and summary of SMIs and outcomes*

232 SMIs and outcomes identified in the RCTs will be described and summarised to provide  
233 information on type and number of interventions, outcome results, patient  
234 characteristics, and presence of comorbidities for each of the four conditions.

#### 235 **Phase 4: Systematic review: NMA and certainty of evidence**

##### 236 • *Network meta-analysis*

237 We will initially develop theoretical models that make explicit the mechanisms through  
238 which the different SMIs operate on a given outcome. Based on our taxonomy of  
239 interventions, these models will identify hierarchies of elements (type of support  
240 provided, expected self-management behaviour, mode of delivery of the intervention,  
241 provider, etc.) that operate on the outcome to identify which components or which  
242 combinations of components are most effective.

243 Additionally to the standard NMA models, we will employ component NMA (35–37) to  
244 identify key intervention components and create a ranking of SMIs according to their  
245 effectiveness. During this process, it is crucial that major assumptions of NMA like  
246 transitivity (that there must be no relevant discrepancy or inconsistency between  
247 direct and indirect evidence(38)) are satisfied, as the validity of results will depend on  
248 the plausibility of the assumptions made. We will also explore the distribution of effect  
249 modifiers (e.g., comorbidities, gender, and socioeconomic factors) across the various  
250 comparisons. This will include differentiation, if possible, between the various forms of  
251 ‘usual care’ reported in the included studies.

##### 252 • *Evaluation and summary of the certainty of the evidence*

253 To guide users in knowing how much confidence they can place in the summarised  
254 evidence; we will rate the certainty of evidence, obtained through the network meta-  
255 analysis, for each outcome of interest, using the Grading of Recommendations,  
256 Assessment, Development and Evaluations (GRADE) approach(39–41). Additionally, we  
257 will apply an alternative approach, the CIneMA framework, to assess the confidence in  
258 the results by exploring how information flows in the network and how much studies  
259 at high/unclear risk of bias affect the network meta-analysis estimates. We will explore  
260 how the assessment differs between these two approaches.

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#### 262 **Phase 5: Model the Cost-effectiveness of effective SMIs**

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4 263 For the cost-effectiveness analysis, data on short term effects on intermediate  
5 264 outcomes (e.g. BMI, HbA1C) from the NMA will serve as input for simulation models  
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7 265 that extrapolate these effects into long term health effects expressed in Quality  
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9 266 Adjusted Life Years (QALYs). These health benefits will be combined with costs (in 2019  
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11 267 Euro's) to estimate the incremental cost per quality-adjusted life year gained. The  
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13 268 development of the health economic models will follow a stepped approach First a  
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15 269 conceptual model of the disease will be developed, informed by a review of  
16  
17 270 the literature. The conceptual model will inform which statistical techniques and  
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19 271 models to use (e.g., discrete-event models, Markov models, patient level simulation  
20  
21 272 models). These decisions will be guided by good practice guidelines  
22  
23 273 from pharmacoeconomic communities of medical decision making and the  
24  
25 274 International Society for Pharmacoeconomics and Outcomes Research (42) available  
26  
27 275 data and clinical expertise available within the consortium. In all four disease  
28  
29 276 models, the natural course of each of the four study conditions will be  
30  
31 277 modelled with incorporation of background events and disease-specific mortality and  
32  
33 278 morbidity. Intervention costs will take into account societal, healthcare, and patient  
34  
35 279 perspectives, and where possible, special attention will be given to societal costs that  
36  
37 280 have historically been understudied (e.g., productivity gains and changes in caregiver  
38  
39 281 burden and costs in life-years gained (37). By expressing health benefits in QALYs we  
40  
41 282 will be able to produce a ranking of the most cost-effective SMIs, within and across  
42  
43 283 conditions. The base cases for the models will have a societal perspective, a life-time  
44  
45 284 time horizon, apply differential discounting at 4% for costs and 1.5% for health (with  
46  
47 285 sensitivity analysis for equal discounting at 3%). The incremental cost-effectiveness  
48  
49 286 ratio's will be evaluated against a so-called v-threshold that denotes willingness to pay  
50  
51 287 for a QALY (43). The WTP in the base case is assumed to be the median WTP of  
52  
53 288 €24,226,- per QALY as found in the systematic review on WTP thresholds by Ryen &  
54  
55 289 Svensson (2015), with sensitivity analyses using the mean WTP threshold from that  
56  
57 290 same review of € 74,159, (44) and country specific thresholds where available.  
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59 291 Reporting will include scenario analyses to evaluate structural uncertainty as well as  
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292 univariate and probabilistic sensitivity analysis to evaluate parameter uncertainty.



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4 294 **Phase 6: Analyse the contextual factors that promote implementation in real life**  
5 295 **contexts**

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7 296 For each of the most effective SMIs identified for the four chronic conditions we will  
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9 297 perform a realist systematic review (45) to identify key determinants of success (or  
10  
11 298 failure), such as intervention settings (e.g., whether on a primary care level or hospital  
12  
13 299 level care) and mechanisms (e.g., engagement processes) that produce specific  
14  
15 300 outcomes. At the patient level, special attention will be paid to comorbidities, gender,  
16  
17 301 and socioeconomic dimensions such as health literacy to better understand how these  
18  
19 302 influence the implementation of the selected SMIs. We will then use a modified Delphi  
20  
21 303 method, with experts on self-management and/or implementation of healthcare  
22  
23 304 interventions, to establish the importance of these contextual factors in the target  
24  
25 305 countries (Belgium, Germany, Greece, the Netherlands & Spain,). Experts will be asked  
26  
27 306 to rate the magnitude of the influence of a contextual factor of a list developed by  
28  
29 307 researchers. The final list of the contextual factors will be produced in a final expert  
30  
31 308 discussion.

31 309 **Phase 7: Development and piloting of the COMPAR-EU information technology platform, and**  
32 310 **preparation for future implementation**

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34  
35 311 We will develop an online platform that will integrate all the information and evidence  
36  
37 312 synthesised during the different phases of the project. The aim is that the resources  
38  
39 313 included facilitate decision making for target end users (patients, healthcare  
40  
41 314 professionals, policymakers, researchers, and small and medium-sized enterprises  
42  
43 315 (SMEs)). The platform will include the following GRADE-based tools:

- 44  
45 316 - Evidence profiles and Interactive Summary of Findings (iSoF) tables(46): these  
46  
47 317 presentations will provide information in different formats about the quality of  
48  
49 318 evidence, and magnitude of relative and absolute effects for each of the core  
50  
51 319 outcomes identified.
- 52 320 - Evidence to Decision frameworks (EtD): using semi-automatic templates,  
53  
54 321 interactive EtD frameworks (47) will be completed for a number of priority  
55  
56 322 questions that will take into account the magnitude of desirable and  
57  
58 323 undesirable effects, stakeholder views on the importance of different  
59  
60 324 outcomes, information on resource use and cost-effectiveness, impact on

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4 325 equity, and other aspects like acceptability or feasibility of the interventions.  
5 326 The frameworks will include draft recommendations that could be then applied  
6  
7 327 or adapted to different settings.

8  
9 328 - Patient decision aids: will be developed in plain-language for all selected  
10  
11 329 situations identified in the previous phases of the study. The aids will be  
12  
13 330 produced in six languages (English, French, German, Spanish, Dutch, and Greek)  
14  
15 331 and will include information obtained in some of the phases included in the  
16  
17 332 project.

18 333 • *Development of COMPAR-EU online platform*

19  
20 334 The COMPAR-EU online platform will feature structured interfaces tailored to the  
21  
22 335 needs of different end users. It will be designed so that after answering a few simple  
23  
24 336 questions, users will be guided to the tool or product that best suits their needs (Figure  
25  
26 337 2 illustrates the main products to be integrated into the platform and expected end-  
27  
28 338 users).

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31 340 *Figure 2. COMPAR-EU Platform, decision-making tools and other end products*

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36 342 • *Piloting and refinement of decision-making tools with different stakeholders*

37  
38 343 The COMPAR-EU platform will be piloted to gauge potential barriers to its  
39  
40 344 implementation and understand how to position the decision-making tools in the  
41  
42 345 target healthcare markets. Decision aids will be piloted among patients and health  
43  
44 346 professionals and EtD frameworks and other products will be piloted with other  
45  
46 347 stakeholders (e.g., policymakers, industry, and representatives of patient associations)  
47  
48 348 that may be involved in implementing the tools in the five participating countries.  
49  
50 349 Piloting will be organised in focus groups and user experience tests in simulated  
51  
52 350 settings using techniques such as thinking-out-loud. Pilots with patient associations  
53  
54 351 and clinicians will focus on the actual use of the decision aids, where pilots with  
55  
56 352 industry and policy makers will focus on the potential reimbursement and integration  
57  
58 353 into existing IT tools.

59 354 Results of the piloting will be used to further improve the tools.  
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4 355 • *Preparation of future implementation*

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6 356 Even with well-developed and user-friendly decision-tools, integration in existing  
7  
8 357 policy and regulatory frameworks is crucial for successful uptake of our  
9  
10 358 recommendations. Using expert networks, we will assess the grey literature, current  
11  
12 359 guidelines and legislation to identify and analyse relevant policy and regulatory  
13  
14 360 frameworks and standards on patient participation, health technology assessment  
15  
16 361 agencies, eHealth/mHealth and other topics that might influence the uptake of the  
17  
18 362 self-management and decision-making tools designed within COMPAR-EU. The  
19  
20 363 purpose is to ensure that current legislative, regulatory and reimbursement decisions  
21  
22 364 at EU level are appropriately considered in exploiting the results of the COMPAR-EU  
23  
24 365 project. We will also hold workshops with industry, pharma, and SMEs to identify  
25  
26 366 business opportunities resulting from the research findings that could result in long-  
27  
28 367 term sustainable dissemination.

29 368 **PATIENT AND PUBLIC INVOLVEMENT**

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31  
32 369 Patients are a key component of the COMPAR-EU project from start to finish and their  
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34 370 interests are represented by the European Patient Forum (EPF), which is one of the  
35  
36 371 consortium partners. Together with other stakeholders, they will be involved in  
37  
38 372 different aspects of the project including prioritisation of core outcomes and testing of  
39  
40 373 interactive tools. A core group of partners, led by the EPF, will also be created to  
41  
42 374 ensure co-production and establishment of explicit criteria to incorporate patient  
43  
44 375 views into project outcomes, products, and communication interventions. Plain-  
45  
46 376 language material will also be developed to support the main end products of the  
47  
48 377 project.

49 378 **ETHICS AND DISSEMINATION**

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52 379 The project coordinator's (Avedis Donabedian Research Institute) requested the  
53  
54 380 overall ethical approval for the project to our local Clinical Research Ethics Committee  
55  
56 381 (CEIC) (the University Institute for Primary Care Research - IDIAP Jordi Gol). Ethical  
57  
58 382 approval was granted on March 2018. Results are of interest to several stakeholder  
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60 383 groups (patients, professionals, managers, policymakers and industry) and will be

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4 384 disseminated in a tailored multi-pronged approach, including the creation of an  
5 385 interactive platform. The data generated by the project will be managed following the  
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7 386 Golden Open access as defined by the European Commission for Horizon 2020  
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9 387 research projects (48).

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15 389 DATA SHARING STATEMENT

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18 390 COMPAR-EU project will make all its anonymized data available upon reasonable  
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20 391 request; where required this will be at aggregated level. The main data dictionaries  
21  
22 392 and databases generated by the project will be available upon requests for uses  
23  
24 393 related to research and quality improvement, and potentially for commercial  
25  
26 394 exploitation, subject to approval by the consortium. Data availability and access is  
27  
28 395 governed by the COMPAR-EU Data Management Plan which is aligned with the EU  
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30 396 Open Data Initiative and the FAIR Principles(49). Further details and information on  
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32 397 how to access the data will be available from COMPAR-EU's project website  
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35 398 (<https://self-management.eu/>).

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400 **LIST OF ABBREVIATIONS**

401 COS – Core Outcome Sets

402 EPF – European Patient Forum

403 NMA – Network meta-analysis

404 SMIs – Self-management interventions

405 RCT – Randomised Control Trial

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3 407 **DECLARATIONS**  
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6 408 **PATIENT AND PUBLIC INVOLVEMENT**  
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9 409 European Patients Forum (EPF) a key umbrella organization in patient representation  
10 410 and European level is a partner of this project and as such has contributed to the  
11 411 project from its inception and design.  
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15  
16 412 Furthermore we have planned for patient participation in key stages of the project,  
17 413 including the selection of outcomes for the Core Outcome Sets, advise towards patient  
18 414 end products and participating in the design and piloting of the COMPAR-EU platform  
19 415 and related decision making tools.  
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27 417 **FIGURE CAPTIONS**  
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30 418 *Figure 1. COMPAR-EU Phases and main tasks*, presents a visual summary of the main  
31 419 phases of the project as described in this protocol.  
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37 421 *Figure 2. COMPAR-EU Platform*, decision-making tools and other end products,  
38 422 presents a visual summary of the projects' foreseen main products and how they  
39 423 relate to the key stakeholders.  
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50 426 **AUTHORS' CONTRIBUTIONS**  
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52  
53 427 • Marta Ballester contributed to the design of the project and prepared the  
54 428 manuscript of the paper.  
55

56  
57 429 • Carola Orrego, Monique Heymans, Pablo Alonso-Coello, Matthijs Versteegh,  
58 430 Dimitris Mavridis, Oliver Groene, Kaisa Immonen, Cordula Wagner, Carlos  
59  
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4 431 Canelo and Rosa Suñol contributed to the design of the project and reviewed  
5 432 and contributed to the manuscript of the paper.  
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13

14 435 **Acknowledgments relating to this study**  
15

16  
17 436 The COMPAR-EU group:  
18  
19

20 437 Ana Isabel González (Fundación Avedis Donabedian, Avedis Donabedian Research  
21  
22 438 Institute (FAD) and REDISSEC), Aretj-Angeliki Veroniki (University of Ioannina,  
23  
24 439 Department of Primary Education), Claudia Valli (Iberoamerican Cochrane Centre –  
25  
26 440 Biomedical Research Institute Sant Pau (IIIB Sant Pau)) Claudio Alfonso Rocha  
27  
28 441 Calderón (Iberoamerican Cochrane Centre – Biomedical Research Institute Sant  
29  
30 442 Pau (IIIB Sant Pau)), Ena Niño de Guzmán (Iberoamerican Cochrane Centre –  
31  
32 443 Biomedical Research Institute Sant Pau (IIIB Sant Pau)), Estela Camus ((Fundación  
33  
34 444 Avedis Donabedian, Avedis Donabedian Research Institute (FAD)), Giorgos Seitidis  
35  
36 445 (University of Ioannina, Department of Primary Education), Hector Pardo-  
37  
38 446 Hernandez (Iberoamerican Cochrane Centre – Biomedical Research Institute Sant  
39  
40 447 Pau (IIIB Sant Pau) and CIBER de Epidemiología y Salud Pública (CIBERESP)), Jany  
41  
42 448 Rademakers (Netherlands Institute for Health Services Research, (NIVEL)), Jessica  
43  
44 449 Beltrán (Iberoamerican Cochrane Centre – Biomedical Research Institute Sant Pau  
45  
46 450 (IIIB Sant Pau)), Karla Salas (Iberoamerican Cochrane Centre – Biomedical Research  
47  
48 451 Institute Sant Pau (IIIB Sant Pau)), Kevin Pacheco-Barrios (Fundación Avedis  
49  
50 452 Donabedian, Avedis Donabedian Research Institute (FAD)), Lyudmil Ninov  
51  
52 453 (European Patients' Forum), Maria Petropoulou (University of Ioannina,  
53  
54 454 Department of Primary Education), Marieke van der Gaag (Netherlands Institute  
55  
56 455 for Health Services Research, (NIVEL)), Montserrat León (Iberoamerican Cochrane  
57  
58 456 Centre – Biomedical Research Institute Sant Pau (IIIB Sant Pau)), Nina Adrion  
59  
60 457 (OptiMedis AG), Rune Poortvliet (Netherlands Institute for Health Services  
458  
Research, (NIVEL)), Stella Zevgiti (University of Ioannina, Department of Primary

1  
2  
3  
4 459 Education), Valentina Strammiello (European Patients' Forum) for their valuable  
5 460 assistance in conducting this proposal.  
6  
7

8 461 • Funding: This work was supported by European Union's Horizon 2020 research  
9  
10 462 and innovation programme under grant agreement No 754936  
11

12 463 • Competing interest statement: no competing interests.  
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For peer review only

Based on previous research  
+ Validated (through expert consultation)

Based on previous research and review of existing COS  
Prioritisation outcomes based on patients' (and other stakeholders) priorities

Phase 3. Systematic review and synthesis of the evidence

Preparation for data collection  
Protocol, training, reviewers agreement

Literature search and screening  
Update fo existing searches and extension

Data extraction and collection  
(approx. 4000 RCTs)

Descriptive analysis and summary

Phase 4: Evaluating and ranking the effectiveness of SMIs through NMA

Network meta-analysis  
(relative intervention effects and ranking of SMIs)  
+  
Subgroup analysis

Evaluation and summary of certainty of the evidence

(of the most effective interventions)

Phase 5: Model the cost-effectiveness of effective SMIs

Phase 6: Analyse the contextual factors that promote implementation in real life contexts

*Metasynthesis of qualitative studies + evaluation of implementation issues*

Phase 7: Development and piloting of the COMPAR-EU information technology platform and preparation for future implementation

Ranking of effective SMIs  
List of most cost-effective SMIs  
Report on contextual factors  
COS  
Taxonomy of SMIs

Icon: People with question mark  
Patient Decision Aids

Development of COMPAR-EU platform  
Icon: Laptop with globe

Icon: Network of nodes  
Interactive Summary of Findings

Icon: People  
Evidence to Decision frameworks

Piloting and refining of COMPAR-EU platform and decision tools  
For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Preparation of future implementation

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