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# BMJ Open

## Reproducible research practices, openness and transparency in health economic evaluations: study protocol for a cross-sectional comparative analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034463
Article Type:	Protocol
Date Submitted by the Author:	20-Sep-2019
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Keywords:	Cost-effectiveness analysis, Data sharing, Methodology, Quality, Reporting, Reproducibility

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1 **Reproducible research practices, openness and transparency in health**  
2 **economic evaluations: study protocol for a cross-sectional comparative**  
3 **analysis**

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3 44 **Abstract**

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5 45 **Introduction**

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7 46 There has been a growing awareness of the need for rigorously and transparent  
8 47 reported health research, to ensure the reproducibility of studies by future  
9 48 researchers. Health economic evaluations, the comparative analysis of alternative  
10 49 interventions in terms of their costs and consequences, have been promoted as an  
11 50 important tool to inform decision-making. The objective of this study will be to  
12 51 investigate the extent to which articles of economic evaluations of healthcare  
13 52 interventions indexed in MEDLINE® incorporate transparency, openness and  
14 53 reproducibility research practices.  
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18 55 **Methods and analysis**

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20 56 This is the study protocol for a cross-sectional comparative analysis. We will evaluate a  
21 57 600 random sample of cost-effectiveness analyses, a specific form of health economic  
22 58 evaluations, indexed in MEDLINE® during 2012 (n=200), 2019 (n=200) and 2022  
23 59 (n=200). We will include published papers written in English reporting an incremental  
24 60 cost-effectiveness ratio in terms of costs per life years gained, quality-adjusted life  
25 61 years, and/or disability-adjusted life years. Screening and selection of articles will be  
26 62 conducted by at least two researchers. Potential discrepancies will be resolved via  
27 63 discussion. Reproducible research practices, openness and transparency in each article  
28 64 will be extracted using a standardized data extraction form by multiple researchers,  
29 65 with a 33% random sample (n=200) extracted in duplicate. Information on general,  
30 66 methodological and reproducibility items will be reported, stratified by year, citation of  
31 67 the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement  
32 68 and journal. Risk ratios with 95% confidence intervals will be calculated to represent  
33 69 changes in reporting between 2012-2019, and 2019-2022.  
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39 70 **Ethics and dissemination**

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41 71 Due to the nature of the proposed study, no ethical approval will be required. All data  
42 72 will be deposited in a cross-disciplinary public repository. It is anticipated the study  
43 73 findings could be relevant to a variety of audiences. Study findings will be disseminated  
44 74 at scientific conferences and published in peer-reviewed journals.  
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47 75 **Keywords**

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49 76 Cost-effectiveness analysis; Data sharing; Methodology; Quality; Reporting;  
50 77 Reproducibility.  
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3 79 **Strengths and limitations of this study**  
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- 5 80 • To our knowledge, this will be the first attempt to examine the extent to which  
6 81 health economic evaluations indexed in MEDLINE® incorporate transparency,  
7 82 openness and reproducibility research practices.
- 83 • We will be able to collect data on a broad cross-section of health economic  
84 84 evaluations and will not restrict inclusion based on the medical specialty,  
85 85 disease condition or healthcare intervention.
- 86 • Study findings could potentially be used to strengthen Open Science strategies  
87 87 and recommendations to increase the value of health economic evaluations.
- 88 • A potential limitation could be the study will include only articles catalogued in  
89 89 one database and written in English.
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## 90 Introduction

91 In recent years, there has been a growing awareness of the need for rigorously and  
92 transparently reported health research, to ensure that studies can be reproduced [1-  
93 7]. The value of health research can be improved by increasing transparency and  
94 openness of the processes of research design, conduct, analysis and reporting [8,9].  
95 Sharing data and materials from health research studies with others is part of good  
96 publication practice, is in keeping with Open Science, and allows for the conduct of  
97 additional analyses, inclusion of unpublished data, reproducing published findings, and  
98 conducting analyses to generate new hypotheses [10]. Journals are increasingly  
99 supporting the use of reporting guidelines, as well as policies and technologies that  
100 help to improve open research culture [11-13]. Scientists are increasingly encouraged  
101 to use reproducible research practices, which allow others to redo the same analysis  
102 (e.g. direct replication) using the same data and analytic methods [14,15]. Research  
103 funders are changing their grant requirements including open data sharing [16,17].

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105 Health economic evaluations, which compare alternative interventions or programmes  
106 in terms of their costs and consequences [18], can help inform resource allocation  
107 decisions. Cost-effectiveness analysis, a specific form of economic evaluation involving  
108 the comparisons of alternative options in terms of their costs and their health  
109 outcomes, is a valuable tool in health technology assessment processes. Cost-  
110 effectiveness analysis has been promoted as an important research methodology for  
111 assessing value for money of healthcare interventions and an important source of  
112 information for making clinical and policy decisions [19]. Decisions about the use of  
113 new interventions in healthcare are often based on health economic evaluations.  
114 Efforts to increase transparent conduct and reporting of health economic evaluations  
115 have existed for many years [20-30]. For example, the Consolidated Health Economic  
116 Evaluation Reporting Standards (CHEERS) statement [30], first published in March  
117 2013, provides recommendations for authors, peer reviewers and journal editors  
118 regarding how to prepare reports of health economic evaluations. The aim of CHEERS  
119 is to facilitate complete and transparent reporting of health economic evaluations and  
120 help more formal critical appraisal and interpretation. As a potential measure of  
121 impact [31], CHEERS has been cited over 1000 times in the Web of Science. However,  
122 little attention has been given to reproducibility practices such as sharing of study  
123 protocols, data and analytic methods (which allow others to recreate the study  
124 findings) as part of health economic evaluation studies [22-25,29].

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126 Jefferson et al. [32] previously investigated whether publication (in August 1996) of the  
127 BMJ guidelines on peer review of economics submissions made any difference to  
128 editorial and peer review processes, quality of submitted manuscripts, and quality of  
129 published manuscripts in two high-impact factor medical journals (The BMJ and The  
130 Lancet). In a sample of 105 articles on economics submissions, 27 (24.3%) were full  
131 health economic evaluations. Although Jefferson et al. [32] were not studying  
132 reproducibility, openness and transparency directly, they did undertake an assessment  
133 of the impact of a reporting guideline for health economic evaluations. Based on a  
134 'before and after' assessment of how closely the reporting guidelines were followed,  
135 they found that the publication of the guidelines helped the editors improve the

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3 136 efficiency of the editorial process but had no impact on the reporting quality of health  
4 137 economic evaluations submitted or published.

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7 139 The primary objective of this study will be to examine the extent to which articles of  
8 140 health economic evaluations of healthcare interventions indexed in MEDLINE®  
9 141 incorporate transparency, openness and reproducibility research practices. Secondary  
10 142 objectives will be to explore (1) how the reporting and reproducibility characteristics of  
11 143 health economic evaluations change between 2012 and 2022, and (2) whether the  
12 144 transparency and reproducibility practices have improved after the publication of the  
13 145 CHEERS statement in 2013.

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## 18 147 **Methods and analysis**

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20 148 This is the study protocol for a cross-sectional, comparative analysis.

### 21 149 *Eligibility criteria*

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23 150 We will evaluate a random sample of 600 cost-effectiveness and cost-utility analyses of  
24 151 healthcare interventions, indexed in MEDLINE® during 2012 (n=200), 2019 (n=200) and  
25 152 2022 (n=200), which focus on a healthcare intervention in humans and reports an  
26 153 incremental cost-effectiveness ratio in terms of costs per life years gained, quality-  
27 154 adjusted life years or disability-adjusted life years. In particular, this analysis focuses on  
28 155 full health economic evaluations that measures health effects in terms of prolongation  
29 156 of life, and/or health-related quality of life. We will select this specific form of health  
30 157 economic evaluations because many decision-makers and researchers have  
31 158 recommended this framework as the standard reference for cost-effectiveness in  
32 159 health and medicine [19]. Publications of health economic evaluations will be limited  
33 160 to journal articles written in English with an abstract available.

34 161 We will exclude editorials, letters, narrative reviews, systematic reviews, meta-  
35 162 analysis, methodological articles, retracted publications, and health economic  
36 163 evaluations that do not quantify health impacts in terms of life years gained, quality-  
37 164 adjusted life years or disability-adjusted life years.

### 38 165 *Searching*

39  
40 166 To provide a reliable summary of the literature, we will search MEDLINE® through  
41 167 PubMed (National Library of Medicine, Bethesda, Maryland, United States) for  
42 168 candidate studies throughout three cross-sectional, comparative time periods. First,  
43 169 we will search MEDLINE®-indexed articles in 2019 (“reference year”) as it is the year  
44 170 closest to when the protocol for this study was drafted. In part two, we will search for  
45 171 articles indexed in 2012 and 2022, respectively, in order to further assess whether the  
46 172 transparency and reproducibility practices improved between 2012 (as it is one year  
47 173 before the publication of the CHEERS statement in 2013 [30]), and 2022 (10 years  
48 174 after). The literature searches will be conducted by an experienced information  
49 175 specialist. Our main literature search will be peer-reviewed by a senior health



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3 176 information specialist using the Peer Review of Electronic Search Strategies (PRESS)  
4 177 checklist [33]. The draft literature search strategy is based on a MEDLINE® search filter  
5 178 for economic evaluations [34], and can be found online in the supplementary appendix  
6 179 1.

### 9 180 *Screening*

11 181 All titles and abstracts will be screened using liberal acceleration (where two reviewers  
12 182 need to independently exclude a record while only one reviewer needs to include a  
13 183 record). We will retrieve the full-text of any citations meeting our eligibility criteria or  
14 184 for which eligibility remains unclear. A form for screening full text articles will be pilot-  
15 185 tested on fifty articles. Subsequently, at least 2 reviewers will independently screen all  
16 186 full text articles. Any discrepancies in screening of titles and abstracts and full-text  
17 187 articles will be resolved via discussion or adjudication by a third reviewer if necessary.

### 21 188 *Data extraction*

23 189 If more than 600 health economic evaluations are identified in the search, we will  
24 190 perform data extraction on a random sample of articles stratified by publication year  
25 191 (200 in 2022, 2019 and 2012, respectively). We will not perform any sample size  
26 192 calculations since our study will evaluate multiple indicators that are considered all  
27 193 equally important, and they may vary substantially in the proportion to which they are  
28 194 satisfied already by the included articles. However, 200 articles per year was assumed  
29 195 to be sufficient to capture potential differences.

33 196 Data in each article will be extracted using a standardized data extraction form by  
34 197 multiple researchers, with a 33% random sample (n=200) extracted in duplicate. All  
35 198 data extractors will independently pilot-test the form on thirty included studies to  
36 199 ensure consistency in interpretation of data items. Subsequently, data from each study  
37 200 will be independently extracted by one of several reviewers. Any discrepancies in the  
38 201 data extracted will be resolved via discussion or adjudication by a third researcher if  
39 202 necessary. Full articles and supplementary materials with data and analyses will be  
40 203 examined for general and methodological characteristics, statements of publicly  
41 204 available full protocols and data sets, conflicts of interest and funding disclosures. In  
42 205 particular, we will review the final versions of the articles available online.

46 206 The selection and wording of general, methodological and reproducibility indicators  
47 207 will be influenced by recommendations in relevant articles on research transparency  
48 208 and reproducibility [4,5,7,8,29,35-37]. The standardized data extraction form will  
49 209 include the following:

52 210 *General characteristics*: name of journal; journal impact factor (according to the latest  
53 211 Journal Citation Report [JCR] at the time of data extraction); journal type (fully-open  
54 212 access journal or subscription-based journal including those that may have open access  
55 213 content e.g., hybrid); year of publication; name, gender and country of corresponding  
56 214 author; type of condition addressed by the economic evaluation (ICD-10 category);  
57 215 type of interventions addressed (pharmacological, nonpharmacological, both) and the

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3 216 intervention to which it was compared (the “comparator”); type of economic  
4 217 evaluation (single-study based economic evaluation or model-based economic  
5 218 evaluation); discussed model calibration and validation (when applicable); results  
6 219 including number of ICERs, sensitivity analysis, subgroup or heterogeneity analyses  
7 220 (e.g. variations between subgroups of patients with different baseline characteristics,  
8 221 or other variability in effects), incremental costs and outcomes for base case analysis  
9 222 ICERs (defined as a qualitative representation of the index ICER e.g. “more costs, more  
10 223 outcomes”, “less costs, more outcomes”, “less costs, comparable outcomes”), the  
11 224 cost-effectiveness ratio values (defined as quantitative representation of the base case  
12 225 analysis ICER), incremental costs (the ratio’s numerator) and health effects (life years  
13 226 gained, quality-adjusted life years or both – the ratio’s denominator for base case  
14 227 analysis); conclusions including favourable if the intervention clearly claims to be the  
15 228 preferred choice (e.g. cited as “cost-effective”, “reduced costs”, “produced cost  
16 229 savings”, “an affordable option”, “value for money”), unfavourable if the final  
17 230 comments are negative (e.g. the intervention is “unlikely to be cost-effective”,  
18 231 “produced higher costs”, “is economically unattractive” or “exceeded conventional  
19 232 thresholds of willingness to pay”) and neutral or uncertain when the intervention of  
20 233 interest do not surpass the comparator and/or when some uncertainty is expressed in  
21 234 the conclusions.

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29 235 *Enablers for reproducibility, transparency and openness*: citation of CHEERS statement  
30 236 (no citation, citation without reporting checklist, citation with reporting checklist); use  
31 237 of CHEERS such as appropriate use (e.g. when CHEERS was used as a reporting  
32 238 guideline to ensure a clear report of the study’s design, conduct and findings),  
33 239 inappropriate use (e.g. when CHEERS was used as a methodological tool to design or  
34 240 conduct health economic evaluations or as an assessment tool of methodological  
35 241 quality of publications reporting cost-effectiveness research), unclear or neutral (e.g.  
36 242 when use was neither appropriate nor inappropriate) [31,38]; open access or  
37 243 availability of free access in PubMed Central (PMC) based on assignment of an specific  
38 244 ID (PMCID) (yes, no); funding (no statement, no funding, public, private, other,  
39 245 combination of public/private/other); conflicts of interests (no statement, statement  
40 246 no conflicts exist, statement conflicts exist); protocol/registration mentioned (no  
41 247 protocol, full protocol publicly available, full protocol publicly available and  
42 248 preregistered); mention of raw data availability (no data sharing, indicated that raw  
43 249 data were available on request, full access to raw data for reanalysis); mention of  
44 250 access to analytic methods and algorithms (e.g. “code”, “script”, “model”) used to  
45 251 perform analyses (no access, indicated that analytic methods were available on  
46 252 request, full access to analytic methods for reanalysis); data repository used, if  
47 253 appropriate including an open globally-scoped repository (e.g. Open Science  
48 254 Framework, Dryad, Mendeley, Zenodo), a journal repository (e.g. supplementary  
49 255 appendix or data paper), other (e.g. repository from a specific institution, project, or  
50 256 nation); reported the data to recreate the index ICERs (base case); reported the data to  
51 257 recreate all core ICERs (base case and heterogeneity analysis); reported the data to  
52 258 recreate all ICERs (base case, heterogeneity analysis and uncertainty analysis)

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3 259 according to reporting standards [30,37]; undergoing rigorous independent replication  
4 260 and reproducibility checks (e.g. whether the study claimed to be a replication effort in  
5 261 the abstracts and introductions) [4,5]: statement of novel findings (e.g. the cost-  
6 262 effectiveness analysis claims that it presents some novel findings), statement of  
7 263 replication (e.g. the cost-effectiveness analysis clearly claims that it is a replication  
8 264 effort trying to validate previous knowledge, or it is inferred that the cost-effectiveness  
9 265 is a replication trying to validate previous knowledge), statement of novel findings and  
10 266 replication (e.g. the cost-effectiveness analysis claims to be both novel and to replicate  
11 267 previous findings), no statement on novelty or replication (e.g. no statement or an  
12 268 unclear statement about whether the cost-effectiveness analysis presents a novel  
13 269 finding or replication).

#### 18 270 *Data analysis*

20 271 The analysis will be descriptive, with data summarised as frequency for categorical  
21 272 items or median and interquartile range for continuous items. We will characterise the  
22 273 indicators for the period 2012-2022. The proportion of general, methodological and  
23 274 reproducibility indicators will be reported, stratified by year citation use of the CHEERS  
24 275 statement, and journal (e.g. according to whether it is an original CHEERS endorsed  
25 276 journal or not). The draft list of original CHEERS endorsed journals can be found in the  
26 277 supplementary appendix 2. A priori established Fisher's exact tests and risk ratios with  
27 278 95% confidence intervals will be calculated to represent changes in reporting between  
28 279 2012-2019, and 2019-2022. We will explore whether reproducible research practices  
29 280 are associated with the citation of the CHEERS statement. We will apply the P value <  
30 281 0.005 threshold for statistical significance, with P values 0.05 to 0.005 suggestive  
31 282 [5,39,40].

32 283 All analyses will be performed using Stata version 15 or higher (StataCorp LP, College  
33 284 Station, Texas, USA).

#### 36 285 **Patient and public involvement**

37 286 No patients and/or public were involved in setting the research question, nor they  
38 287 were involved in developing plans for design (or implementation) of this study  
39 288 protocol. No patients and/or public will be asked to advice on the interpretation or  
40 289 writing up of results. There are no specific plans to disseminate the results of the  
41 290 research to the patient community.

#### 42 291 **Ethics and dissemination**

43 292 To the best of our knowledge, this cross-sectional analysis will be the first attempt to  
44 293 investigate the extent to which articles of cost-effectiveness of healthcare  
45 294 interventions incorporate transparency, openness and reproducibility research  
46 295 practices. We anticipate the study could be relevant to a variety of audiences including  
47 296 journal editors, peer reviewers, research authors, health technology assessment  
48 297 agencies, guideline developers, research funders, educators and other potential key  
49 298 stakeholders. Moreover, the study findings could further be used in discussions to

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3 299 strengthen Open Science in order to increase value and reduce waste from incomplete  
4 300 or unusable reports of health economic evaluations.

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6 301 Any amendments made to this protocol when conducting the analyses will be outlined  
7 302 and reported in the final manuscript. Findings from this study will be published in peer-  
8 303 reviewed journals. All data underlying the findings reported in the final manuscript will  
9 304 be deposited in a cross-disciplinary public repository, such as the Open Science  
10 305 Framework (<https://osf.io/>).

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15 307 **Abbreviations:**

16 308 CHEERS: Consolidated Health Economic Evaluation Reporting Standards

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18 309 ICD-10: International Statistical Classification of Diseases and Related Health Problems,  
19 310 10<sup>th</sup> revision

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21 311 ICER: Incremental Cost Effectiveness Ratio

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23 312 JCR: Journal Citation Report

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25 313 PMC: PubMed Central

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27 314 PMCID: PubMed Central ID

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29 315 PRESS: Peer Review of Electronic Search Strategies

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33 317 **Ethical approval:** This manuscript outlines a protocol for a cross-sectional analysis that  
34 318 will undertake secondary data analysis and hence does not require ethical approval.

35  
36 319 **Contributors:** All authors contributed to conceptualizing and designing the study. FC-L  
37 320 drafted the manuscript. LC, MR, BH, DH, MFD, AA-A, MP-F, EB-D, RM, RT-S, JRR, and  
38 321 DM commented for important intellectual content and made revisions. All authors  
39 322 read and approved the final version of the manuscript. FC-L accepts full responsibility  
40 323 for the finished manuscript and controlled the decision to publish.

41  
42 324 **Funding:** FC-L and RT-S are supported by the Institute of Health Carlos III/CIBERSAM.  
43 325 BH is supported by a New Investigator Award from the Canadian Institutes of Health  
44 326 Research and the Drug Safety and Effectiveness Network. MR and EB-D are supported  
45 327 by the Institute of Health Carlos III/Spanish Health Services Research on Chronic  
46 328 Patients Network (REDISSEC). DM is supported by a University Research Chair,  
47 329 University of Ottawa. The funders were not involved in the design of the protocol or  
48 330 decision to submit the protocol for publication, nor will they be involved in any aspect  
49 331 of the study conduct. The views expressed in this manuscript are those of the authors  
50 332 and many not be understood or quoted as being made on behalf of, or reflecting the  
51 333 position of, the funder(s) or any institution.

52  
53 334 **Competing interests:** None declared.  
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**Supplementary Appendix 1.** Draft search for PubMed/MEDLINE®.

1. "cost-benefit analysis"[mh] OR "costs and cost analysis"[mh] OR "cost-effective\*" [ti] OR "cost-utility"[ti]
2. Journal Article[pt] AND hasabstract[text] AND English[lang] AND ("humans"[mh] OR "humans"[All Fields])
3. Editorial[pt] OR Letter[pt] OR Historical Article[pt] OR Meta-Analysis[pt] OR Retracted Publication[sb] OR Review[pt] OR systematic[sb]
4. #1 AND #2
5. #4 NOT #3

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**Supplementary Appendix 2.** Draft list of original CHEERS endorsed journals.

- Applied Health Economics and Health Policy
- BJOG: An International Journal of Obstetrics and Gynaecology
- BMC Medicine
- The BMJ
- British Journal of Psychiatry
- Clinical Therapeutics
- Cost Effectiveness and Resource Allocation
- The European Journal of Health Economics
- International Journal of Technology Assessment in Health Care
- Journal of Medical Economics
- Pharmacoeconomics
- Value in Health

For more information, see: [https://www.ispor.org/heor-resources/good-practices-for-outcomes-research/article/consolidated-health-economic-evaluation-reporting-standards-\(cheers\)---explanation-and-elaboration](https://www.ispor.org/heor-resources/good-practices-for-outcomes-research/article/consolidated-health-economic-evaluation-reporting-standards-(cheers)---explanation-and-elaboration)

# BMJ Open

## Reproducible research practices, openness and transparency in health economic evaluations: study protocol for a cross-sectional comparative analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034463.R1
Article Type:	Protocol
Date Submitted by the Author:	20-Dec-2019
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<b>Primary Subject Heading</b>:	Health economics
Secondary Subject Heading:	Medical publishing and peer review, Public health, Research methods
Keywords:	Cost-effectiveness analysis, Data sharing, Methodology, Quality, Reporting, Reproducibility

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## 1 Reproducible research practices, openness and transparency in health 2 economic evaluations: study protocol for a cross-sectional comparative 3 analysis

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7 José R. Repullo<sup>1</sup>, David Moher<sup>3,7</sup>

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For peer review only

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3 **45 Abstract**

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5 **46 Introduction**

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7 47 There has been a growing awareness of the need for rigorously and transparent  
8 48 reported health research, to ensure the reproducibility of studies by future  
9 49 researchers. Health economic evaluations, the comparative analysis of alternative  
10 50 interventions in terms of their costs and consequences, have been promoted as an  
11 51 important tool to inform decision-making. The objective of this study will be to  
12 52 investigate the extent to which articles of economic evaluations of healthcare  
13 53 interventions indexed in MEDLINE® incorporate research practices that promote  
14 54 transparency, openness and reproducibility.  
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18 **56 Methods and analysis**

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20 57 This is the study protocol for a cross-sectional comparative analysis. We will evaluate a  
21 58 random sample of 600 cost-effectiveness analysis publications, a specific form of  
22 59 health economic evaluations, indexed in MEDLINE® during 2012 (n=200), 2019 (n=200)  
23 60 and 2022 (n=200). We will include published papers written in English reporting an  
24 61 incremental cost-effectiveness ratio in terms of costs per life years gained, quality-  
25 62 adjusted life years, and/or disability-adjusted life years. Screening and selection of  
26 63 articles will be conducted by at least two researchers. Reproducible research practices,  
27 64 openness and transparency in each article will be extracted using a standardized data  
28 65 extraction form by multiple researchers, with a 33% random sample (n=200) extracted  
29 66 in duplicate. Information on general, methodological and reproducibility items will be  
30 67 reported, stratified by year, citation of the Consolidated Health Economic Evaluation  
31 68 Reporting Standards (CHEERS) statement and journal. Risk ratios with 95% confidence  
32 69 intervals will be calculated to represent changes in reporting between 2012-2019, and  
33 70 2019-2022.  
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39 **71 Ethics and dissemination**

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41 72 Due to the nature of the proposed study, no ethical approval will be required. All data  
42 73 will be deposited in a cross-disciplinary public repository. It is anticipated the study  
43 74 findings could be relevant to a variety of audiences. Study findings will be disseminated  
44 75 at scientific conferences and published in peer-reviewed journals.  
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47 **76 Study registration**

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49 77 Open Science Framework ([osf.io/gzaxr](https://osf.io/gzaxr))  
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51 **78 Keywords**

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53 79 Cost-effectiveness analysis; Data sharing; Methodology; Quality; Reporting;  
54 80 Reproducibility.  
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3 82 **Strengths and limitations of this study**  
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- 5 83 • To our knowledge, this will be the first attempt to examine the extent to which  
6 84 health economic evaluations indexed in MEDLINE® incorporate transparency,  
7 85 openness and reproducibility research practices.
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10 86 • We will be able to collect data on a broad cross-section of health economic  
11 87 evaluations and will not restrict inclusion based on the medical specialty,  
12 88 disease condition or healthcare intervention.
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14 89 • Study findings could be used to strengthen Open Science strategies and  
15 90 recommendations to increase the value of health economic evaluations.
- 16  
17 91 • The study may be limited by the inclusion of articles only catalogued in one  
18 92 database and written in English.
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## 93 Introduction

94 In recent years, there has been a growing awareness of the need for rigorous and  
95 transparent reporting of health research, to ensure that studies can be reproduced [1-  
96 7]. The value of health research can be improved by increasing transparency and  
97 openness of the processes of research design, conduct, analysis and reporting [8,9].  
98 Sharing data and materials from health research studies has multiple positive effects  
99 within the research community: it is part of good publication practice, in keeping the  
100 principles of Open Science; it allows for the conduct of additional analyses to further  
101 explore data and generate new hypotheses; it allows access to unpublished data, and  
102 it encourages reproducibility in research [10]. Recognizing the potential impact of open  
103 research culture, journals are increasingly supporting the use of reporting guidelines,  
104 as well as policies and technologies that help to improve transparency [11-13].  
105 Scientists are increasingly encouraged to use reproducible research practices, which  
106 allow others to perform direct replication of studies using the same data and analytic  
107 methods [14,15]. Furthermore, research funders are changing their grant  
108 requirements including open data sharing [16,17].

109  
110 Health economic evaluations, which compare alternative interventions or programmes  
111 in terms of their costs and consequences [18], can help inform resource allocation  
112 decisions. A cost-effectiveness analysis, a specific form of economic evaluation that  
113 compares alternative options in terms of their costs and their health outcomes, is a  
114 valuable tool in health technology assessment processes. Cost-effectiveness analyses  
115 have been promoted as an important research methodology for assessing value for  
116 money of healthcare interventions and an important source of information for making  
117 clinical and policy decisions [19]. Decisions about the use of new interventions in  
118 healthcare are often based on health economic evaluations. Efforts to increase  
119 transparent conduct and reporting of health economic evaluations have existed for  
120 many years [20-30]. For example, the Consolidated Health Economic Evaluation  
121 Reporting Standards (CHEERS) statement [30], first published in March 2013, provides  
122 recommendations for authors, peer reviewers and journal editors regarding how to  
123 prepare reports of health economic evaluations. The aim of CHEERS is to facilitate  
124 complete and transparent reporting of health economic evaluations and help more  
125 formal critical appraisal and interpretation. As a potential measure of impact [31],  
126 CHEERS has been cited over 1000 times in the Web of Science. However, little  
127 attention has been given to reproducibility practices such as sharing of study  
128 protocols, data and analytic methods (which allow others to recreate the study  
129 findings) as part of health economic evaluation studies [22-25,29].

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131 Previous research has evaluated the impact of economic evaluation guidelines and the  
132 reporting quality of published articles. For example, Jefferson et al. [32] previously  
133 investigated whether publication (in August 1996) of the BMJ guidelines on peer  
134 review of economics submissions made any difference to editorial and peer review  
135 processes, quality of submitted manuscripts, and quality of published manuscripts in  
136 two high-impact factor medical journals (The BMJ and The Lancet). In a sample of 105  
137 articles on economics submissions, 27 (24.3%) were full health economic evaluations.  
138 Although Jefferson et al. [32] were not studying reproducibility, openness and  
139 transparency directly, they did undertake an assessment of the impact of a reporting



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3 140 guideline for health economic evaluations. A 'before and after' assessment of  
4 141 implementation of the guideline was performed to assess how closely the reporting  
5 142 guidelines were followed. The authors found that the publication of the guidelines  
6 143 helped the editors improve the efficiency of the editorial process but had no impact on  
7 144 the reporting quality of health economic evaluations submitted or published.  
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9 145

10 146 The primary objective of this study will be to examine the extent to which articles of  
11 147 health economic evaluations of healthcare interventions indexed in MEDLINE®  
12 148 incorporate transparency, openness and reproducibility research practices. Secondary  
13 149 objectives will be to explore (1) how the reporting and reproducibility characteristics of  
14 150 health economic evaluations change between 2012 and 2022, and (2) whether the  
15 151 transparency and reproducibility practices have improved after the publication of the  
16 152 CHEERS statement in 2013.  
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## 21 154 **Methods and analysis**

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24 155 This is the study protocol for a cross-sectional, comparative analysis. The present  
25 156 protocol has been registered within the Open Science Framework (registration  
26 157 identifier: [osf.io/gzaxr](https://osf.io/gzaxr)). It is anticipated the study will be conducted during January  
27 158 2020 to December 2023.  
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29

### 30 159 *Eligibility criteria*

31  
32 160 We will evaluate a random sample of 600 cost-effectiveness and cost-utility analyses of  
33 161 healthcare interventions, indexed in MEDLINE® during 2012 (n=200), 2019 (n=200) and  
34 162 2022 (n=200), which focus on a healthcare intervention in humans and reports an  
35 163 incremental cost-effectiveness ratio in terms of costs per life years gained, quality-  
36 164 adjusted life years or disability-adjusted life years. In particular, this analysis will focus  
37 165 on full health economic evaluations that measures health effects in terms of  
38 166 prolongation of life, and/or health-related quality of life. We will select this specific  
39 167 form of health economic evaluations because many decision-makers and researchers  
40 168 have recommended this framework as the standard reference for cost-effectiveness in  
41 169 health and medicine [19]. Publications of health economic evaluations will be limited  
42 170 to journal articles written in English with an abstract available.  
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47 171 We will exclude editorials, letters, narrative reviews, systematic reviews, meta-  
48 172 analysis, methodological articles, retracted publications, and health economic  
49 173 evaluations that do not quantify health impacts in terms of life years gained, quality-  
50 174 adjusted life years or disability-adjusted life years.  
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### 53 175 *Searching*

54  
55 176 To provide a reliable summary of the literature, we will search MEDLINE® through  
56 177 PubMed (National Library of Medicine, Bethesda, Maryland, United States) for  
57 178 candidate studies throughout three cross-sectional, comparative time periods. First,  
58 179 we will search MEDLINE®-indexed articles in 2019 ("reference year") as it is the year  
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3 180 closest to when the protocol for this study was drafted. In part two, we will search for  
4 181 articles indexed in 2012 and 2022, respectively, in order to further assess whether the  
5 182 transparency and reproducibility practices improved between 2012 (as it is one year  
6 183 before the publication of the CHEERS statement in 2013 [30]), and 2022 (10 years  
7 184 after). The literature searches will be conducted by an experienced information  
8 185 specialist. Our main literature search will be peer-reviewed by a senior health  
9 186 information specialist using the Peer Review of Electronic Search Strategies (PRESS)  
10 187 checklist [33]. The draft literature search strategy is based on a MEDLINE® search filter  
11 188 for economic evaluations [34], and can be found online in the supplementary appendix  
12 189 1.

### 17 190 *Screening*

19 191 All titles and abstracts will be screened using liberal acceleration (where two reviewers  
20 192 need to independently exclude a record while only one reviewer needs to include a  
21 193 record). We will retrieve the full-text of any citations meeting our eligibility criteria or  
22 194 for which eligibility remains unclear. A form for screening full text articles will be pilot-  
23 195 tested on fifty articles. Subsequently, at least 2 reviewers will independently screen all  
24 196 full text articles. Any discrepancies in screening full-text articles will be resolved via  
25 197 discussion or adjudication by a third reviewer if necessary.

### 29 198 *Data extraction*

31 199 If more than 600 health economic evaluations are identified in the search, we will  
32 200 perform data extraction on a random sample of articles stratified by publication year  
33 201 (200 in 2022, 2019 and 2012, respectively). If fewer than 200 articles are identified in a  
34 202 given year (e.g. 2012), we will randomly select the sufficient number of studies  
35 203 published from the preceding year (e.g. October-December 2011) to match the  
36 204 number used in the study sample. We will not perform any sample size calculations  
37 205 since our study will evaluate multiple indicators that are considered all equally  
38 206 important, and they may vary substantially in the proportion to which they are  
39 207 satisfied by the included articles. However, 200 articles per year was assumed to be  
40 208 sufficient to capture potential differences.

44 209 Data in each article will be extracted using a standardized data extraction form by  
45 210 multiple researchers, with a 33% random sample (n=200) extracted in duplicate. All  
46 211 data extractors will independently pilot-test the form on thirty included studies to  
47 212 ensure consistency in interpretation of data items. Subsequently, data from each study  
48 213 will be independently extracted by one of several reviewers. Any discrepancies in the  
49 214 data extracted will be resolved via discussion or adjudication by a third researcher if  
50 215 necessary. Full articles and supplementary materials with data and analyses will be  
51 216 examined for general and methodological characteristics, statements of publicly  
52 217 available full protocols and data sets, conflicts of interest and funding disclosures. In  
53 218 particular, we will review the final versions of the articles available online.

58 219 The selection and wording of general, methodological and reproducibility indicators  
59 220 will be influenced by recommendations from relevant articles on research

221 transparency and reproducibility [4,5,7,8,29,35-41]. The standardized data extraction  
222 form will include the following:

223 *General characteristics:*

- 224 - Name of journal;
- 225 - Journal impact factor (according to the latest Journal Citation Report [JCR] at  
226 the time of data extraction);
- 227 - Journal type (fully-open access journal or subscription-based journal including  
228 those that may have open access content e.g., hybrid);
- 229 - Year of publication;
- 230 - Name, gender and country of corresponding author;
- 231 - Type of condition addressed by the economic evaluation (ICD-10 category);
- 232 - Type of interventions addressed (pharmacological, nonpharmacological, both)  
233 and the intervention to which it was compared (the “comparator” e.g. active  
234 alternative, usual care or placebo/do nothing) with adequate descriptions  
235 [40,41];
- 236 - Type of economic evaluation (single-study based economic evaluation or  
237 model-based economic evaluation);
- 238 - Study perspective (e.g. society, healthcare system/provider) and relate this to  
239 the costs being evaluated;
- 240 - Time horizon over which costs and outcomes are being evaluated;
- 241 - Discount rate used for costs and outcomes with rationale (when applicable);
- 242 - Health outcomes used as the measure of benefit (e.g. life years gained, quality-  
243 adjusted life years or disability-adjusted life years) and their relevance for the  
244 type of analysis performed;
- 245 - Measurement of effectiveness (e.g. for single-study based estimates: a  
246 description of the design features of the single effectiveness study, and why the  
247 single study was a sufficient source of clinical effectiveness; and for synthesis-  
248 based estimates: a description of the methods used for identification of  
249 included studies and synthesis of clinical effectiveness data);
- 250 - Estimate of resources and costs (including a description of approaches used to  
251 estimate resource use associated with the alternative interventions; and  
252 describe methods for valuing each resource item in terms of its unit costs);
- 253 - Discussion of all analytical methods supporting the evaluation (e.g. methods for  
254 dealing with skewed, missing or censored data; extrapolation methods;  
255 methods for pooling data; methods for handling population heterogeneity and  
256 uncertainty such as subgroup analysis); choice of model and model calibration  
257 and validation (when applicable);
- 258 - Results including number of ICERs, sensitivity analyses, subgroup or  
259 heterogeneity analyses (e.g. variations between subgroups of patients with  
260 different baseline characteristics, or other variability in effects), incremental  
261 costs and outcomes for base case analysis ICERs (defined as a qualitative  
262 representation of the index ICER e.g. “more costs, more outcomes”, “less costs,  
263 more outcomes”, “less costs, comparable outcomes”), the cost-effectiveness

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3 264 ratio values (defined as quantitative representation of the base case analysis  
4 265 ICER), incremental costs (the ratio's numerator) and health effects (life years  
5 266 gained, quality-adjusted life years or both – the denominator of the ratio for  
6 267 base case analysis);
- 8 268 - Conclusions including favourable if the intervention clearly claims to be the  
9 269 preferred choice (e.g. cited as “cost-effective”, “reduced costs”, “produced cost  
10 270 savings”, “an affordable option”, “value for money”), unfavourable if the final  
11 271 comments are negative (e.g. the intervention is “unlikely to be cost-effective”,  
12 272 “produced higher costs”, “is economically unattractive” or “exceeded  
13 273 conventional thresholds of willingness to pay”) and neutral or uncertain when  
14 274 the intervention of interest do not surpass the comparator and/or when some  
15 275 uncertainty is expressed in the conclusions.
  - 16 276 - Funding (e.g. no statement, no funding, public, private, other, combination of  
17 277 public/private/other);
  - 18 278 - Conflicts of interests (e.g. no statement, statement no conflicts exist, statement  
19 279 conflicts exist).

20 280 *Enablers for reproducibility, transparency and openness:*

- 21 281 - Citation and/or mention of CHEERS statement (e.g. no citation/mention,  
22 282 citation/mention without reporting checklist, citation/mention with reporting  
23 283 checklist);
- 24 284 - Use of CHEERS appropriately (e.g. when CHEERS was used as a reporting  
25 285 guideline to ensure a clear report of the study's design, conduct and findings),  
26 286 inappropriately (e.g. when CHEERS was used as a methodological tool to design  
27 287 or conduct health economic evaluations or as an assessment tool of  
28 288 methodological quality of publications reporting cost-effectiveness research),  
29 289 or in an unclear or neutral manner (e.g. when use was neither appropriate nor  
30 290 inappropriate) [31,42];
- 31 291 - Open access or free availability in PubMed Central (PMC) based on assignment  
32 292 of an specific ID (PMCID) (yes, no);
- 33 293 - Protocol/registration mentioned (e.g. no protocol, full protocol publicly  
34 294 available, full protocol publicly available and preregistered);
- 35 295 - Health economics analysis plan mentioned (e.g. no analysis plan, indicated that  
36 296 analysis plan was available on request, full access to analysis plan along with  
37 297 research protocol) [39]
- 38 298 - Mention of raw data availability (e.g. no data sharing, indicated that raw data  
39 299 were available on request, full access to raw data for reanalysis);
- 40 300 - Mention of access to analytic methods and algorithms (e.g. “code”, “script”,  
41 301 “model”) used to perform analyses (e.g. no access, indicated that analytic  
42 302 methods were available on request, full access to analytic methods for  
43 303 reanalysis);
- 44 304 - Type of data repository used, if appropriate including use of an open globally-  
45 305 scoped repository (e.g. Open Science Framework, Dryad, Mendeley, Zenodo), a

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3 306 journal repository (e.g. supplementary appendix or data paper), or other  
4 307 repository (e.g. repository from a specific institution, project, or nation);  
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6 308 - Data made available to recreate the index ICERs (base case);  
7 309 - Data made available to recreate all core ICERs (base case and heterogeneity  
8 310 analysis);  
9  
10 311 - Data made available to recreate all ICERs (base case, heterogeneity analysis and  
11 312 uncertainty analysis) according to reporting standards [30,38];  
12 313 - Results have undergone rigorous independent replication and reproducibility  
13 314 checks (e.g. whether the study claimed to be a replication effort in the  
14 315 abstracts and introductions) [4,5]: statement of novel findings (e.g. the cost-  
15 316 effectiveness analysis claims that it presents some novel findings), statement of  
16 317 replication (e.g. the cost-effectiveness analysis clearly claims that it is a  
17 318 replication effort trying to validate previous knowledge, or it is inferred that the  
18 319 cost-effectiveness is a replication trying to validate previous knowledge),  
19 320 statement of novel findings and replication (e.g. the cost-effectiveness analysis  
20 321 claims to be both novel and to replicate previous findings), no statement on  
21 322 novelty or replication (e.g. no statement or an unclear statement about  
22 323 whether the cost-effectiveness analysis presents a novel finding or replication).

#### 27 324 *Data analysis*

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29 325 The analysis will be descriptive, with data summarised as frequency for categorical  
30 326 items or median and interquartile range for continuous items. We will characterise the  
31 327 indicators for the period 2012-2022. The proportion of general, methodological and  
32 328 reproducibility indicators stratified by year will be reported, as well as citation use of  
33 329 the CHEERS statement, and journal (e.g. according to whether it is an original CHEERS  
34 330 endorsed journal or not). The draft list of original CHEERS endorsed journals can be  
35 331 found in the supplementary appendix 2. A priori established Fisher's exact tests and  
36 332 risk ratios with 95% confidence intervals will be calculated to represent changes in  
37 333 reporting between 2012-2019, and 2019-2022. We will explore whether reproducible  
38 334 research practices are associated with the citation of the CHEERS statement. We will  
39 335 apply the P value < 0.005 threshold for statistical significance, with P values 0.05 to  
40 336 0.005 suggestive [5,43,44].

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43 337 All analyses will be performed using Stata version 16 or higher (StataCorp LP, College  
44 338 Station, Texas, USA).

#### 45 46 47 48 49 339 *Updates and additional analyses*

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51 340 We plan to conduct a continual surveillance of the health economic literature, keeping  
52 341 evidence as up-to-date as possible. Iterations of the searches and review process will  
53 342 be repeated at regular intervals (e.g. 3 year intervals after 2022) to continue to present  
54 343 timely and accurate findings. Reanalysis of the proposed reproducibility and  
55 344 transparency metrics and indicators may offer insight into progressive improvements  
56 345 in design, conduct, and analysis of health economic evaluations over time.

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3 346 Any (new) additional analysis examining potential associations between general  
4 347 characteristics from extracted studies (e.g. results including index ICER, or funding  
5 348 source) and enablers of reproducibility, transparency and openness (e.g. mention of  
6 349 CHEERS statement, open access, protocol registration, or mention of raw data) will be  
7 350 prospectively reported in a new specific (sub-study) protocol, following standard  
8 351 methods described in this paper.  
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### 13 353 **Patient and public involvement**

14  
15 354 No patients and/or public were involved in setting the research question, nor they  
16 355 were involved in developing plans for design (or implementation) of this study  
17 356 protocol.  
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### 21 357 **Ethics and dissemination**

22  
23 358 To the best of our knowledge, this cross-sectional analysis will be the first attempt to  
24 359 investigate the extent to which articles of cost-effectiveness of healthcare  
25 360 interventions incorporate transparent, open and reproducible research practices.  
26 361 Without complete and transparent reporting of how a health economic evaluation is  
27 362 being designed and conducted, it is difficult for readers and potential knowledge users  
28 363 to assess its conduct and validity. Strengthening the reproducibility, openness and  
29 364 reporting of methods and results can maximize the impact of health economic  
30 365 evaluations by allowing more accurate interpretation and use of their findings. We  
31 366 anticipate the study could be relevant to a variety of audiences including journal  
32 367 editors, peer reviewers, research authors, health technology assessment agencies,  
33 368 guideline developers, research funders, educators and other potential key  
34 369 stakeholders. Moreover, the study findings could further be used in discussions to  
35 370 strengthen Open Science in order to increase value and reduce waste from incomplete  
36 371 or unusable reports of health economic evaluations.  
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42 372 Any amendments made to this protocol when conducting the analyses will be outlined  
43 373 and reported in the final manuscript. Once completed, findings from this study will be  
44 374 published in peer-reviewed journals. All data underlying the findings reported in the  
45 375 final manuscript will be deposited in a cross-disciplinary public repository, such as the  
46 376 Open Science Framework (<https://osf.io/>). In addition, when new data have become  
47 377 available, we will update the analysis and present the updated findings at a public  
48 378 repository (and we may also seek publication in a peer-reviewed journal).  
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### 53 380 **Abbreviations:**

54 381 CHEERS: Consolidated Health Economic Evaluation Reporting Standards

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56 382 ICD-10: International Statistical Classification of Diseases and Related Health Problems,  
57 383 10<sup>th</sup> revision  
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3 384 ICER: Incremental Cost Effectiveness Ratio  
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5 385 JCR: Journal Citation Report  
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7 386 PMC: PubMed Central  
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9 387 PMCID: PubMed Central ID  
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11 388 PRESS: Peer Review of Electronic Search Strategies  
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13 389

15 390 **Ethical approval:** This manuscript outlines a protocol for a cross-sectional analysis that  
16 391 will undertake secondary data analysis and hence does not require ethical approval.

18 392 **Contributors:** All authors contributed to conceptualizing and designing the study. FC-L  
19 393 drafted the manuscript. LC, MR, BH, DH, MFD, AA-A, MP-F, EB-D, RM, RT-S, JRR, and  
20 394 DM commented for important intellectual content and made revisions. All authors  
21 395 read and approved the final version of the manuscript. FC-L accepts full responsibility  
22 396 for the finished manuscript and controlled the decision to publish.

25 397 **Funding:** FC-L and RT-S are supported by the Institute of Health Carlos III/CIBERSAM.  
26 398 BH is supported by a New Investigator Award from the Canadian Institutes of Health  
27 399 Research and the Drug Safety and Effectiveness Network. MR and EB-D are supported  
28 400 by the Institute of Health Carlos III/Spanish Health Services Research on Chronic  
29 401 Patients Network (REDISSEC). DM is supported by a University Research Chair,  
30 402 University of Ottawa. The funders were not involved in the design of the protocol or  
31 403 decision to submit the protocol for publication, nor will they be involved in any aspect  
32 404 of the study conduct. The views expressed in this manuscript are those of the authors  
33 405 and many not be understood or quoted as being made on behalf of, or reflecting the  
34 406 position of, the funder(s) or any institution.

39 407 **Competing interests:** None declared.  
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**Supplementary Appendix 1.** Draft search for PubMed/MEDLINE®.

1. "cost-benefit analysis"[mh] OR "costs and cost analysis"[mh] OR "cost-effective\*" [ti] OR "cost-utility"[ti] OR "economic evaluation"[ti]
2. Journal Article[pt] AND hasabstract[text] AND English[lang] AND ("humans"[mh] OR "humans"[All Fields])
3. Editorial[pt] OR Letter[pt] OR Historical Article[pt] OR Meta-Analysis[pt] OR Retracted Publication[sb] OR Review[pt] OR systematic[sb]
4. #1 AND #2
5. #4 NOT #3

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**Supplementary Appendix 2.** Draft list of original CHEERS endorsed journals.

- Applied Health Economics and Health Policy
- BJOG: An International Journal of Obstetrics and Gynaecology
- BMC Medicine
- The BMJ
- British Journal of Psychiatry
- Clinical Therapeutics
- Cost Effectiveness and Resource Allocation
- The European Journal of Health Economics
- International Journal of Technology Assessment in Health Care
- Journal of Medical Economics
- Pharmacoeconomics
- Value in Health

For more information, see: [https://www.ispor.org/heor-resources/good-practices-for-outcomes-research/article/consolidated-health-economic-evaluation-reporting-standards-\(cheers\)---explanation-and-elaboration](https://www.ispor.org/heor-resources/good-practices-for-outcomes-research/article/consolidated-health-economic-evaluation-reporting-standards-(cheers)---explanation-and-elaboration)