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Psychometric properties of self-reported financial toxicity measures in cancer survivors: a COSMIN systematic review protocol

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4 1 **Psychometric properties of self-reported financial toxicity measures in cancer**
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6 2 **survivors: a COSMIN systematic review protocol**
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4 20 **Psychometric properties of self-reported financial toxicity measures for cancer**
5 21 **survivors: a COSMIN systematic review protocol**
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9 23 **Abstract**

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11 24 **Introduction:** Due to the higher costs associated with advancements in cancer treatment and
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13 25 longer duration of cancer survivorship, increasing financial toxicity has become a great threat to
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15 26 survivors, caregivers, and public healthcare systems. Since accurate and reproducible measures are
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17 27 prerequisites for robust results, choosing an acceptable measure with strong psychometric properties to
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19 28 assess financial toxicity is essential. However, a description of the psychometric properties of existing
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21 29 measures is still lacking. The aim of this study is to apply COnsensus-based Standards for the selection
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23 30 of health Measurement INstruments (COSMIN) methodology to systematically review the content and
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25 31 structural validity of patient-reported outcome measures (PROMs) of financial toxicity for cancer
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27 32 survivors.
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31 34 **Methods and analysis:** PubMed/MEDLINE, MEDLINE (Ovid), EMBASE (Ovid), CINAHL
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33 35 (EBSCO), Web of Science, ProQuest Dissertations and Theses, and Cochrane Library (Wiley) will be
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35 36 comprehensively searched from database inception to November 15, 2019. Studies that report the
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37 37 measurement properties of PROMs assessing financial toxicity for cancer survivors will be included.
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39 38 The evaluation of measurement properties, data extraction, and data synthesis will be conducted
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41 39 according to the COSMIN methodology.
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45 41 **Ethics and dissemination:** No individual data are involved in this systematic review. The results
46
47 42 will be disseminated to a clinical audience and policy makers through peer-reviewed journals and
48
49 43 conferences and will support researchers in choosing the best measure to evaluate the financial toxicity
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51 44 of cancer survivors.
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53 45

54 46 **Keywords:** cancer; oncology; financial toxicity; systematic review; COSMIN; PROM
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57 48 **Word count:** 2030
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4 50 **Strengths and limitations of this study**

- 5 51 ● This is the first systematic review that will identify generic and cancer-specific patient-reported
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7 52 outcome measures (PROMs) to assess FT for cancer survivors and provide a comprehensive
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9 53 picture of their measurement properties.
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11 54 ● The results will enable guideline developers to better understand the underlying measurement
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13 55 properties of existing PROMs measuring FT for cancer survivors.
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15 56 ● The conclusion may apply only to specific properties of PROMs.
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INTRODUCTION

Given the higher costs associated with advancements in cancer treatment and longer duration of cancer survivorship, the increasing financial burden is currently becoming a great threat to survivors, caregivers, and public healthcare systems.^{1,2} The total global spending on cancer care medicines increased from US\$ 96 billion in 2013 to US\$ 133 billion in 2017 at a compound annual growth rate of 6.5%, which is almost two times larger than the global GDP growth rate.^{3,4} Cancer treatment and survivorship are estimated to cost US\$ 173 billion in 2020.⁵ Notably, middle-income and low-income countries relying on out-of-pocket payments contribute to global disparities in healthcare spending and inequity in financial vulnerability for cancer survivors.^{6,7}

The term “financial toxicity” (FT) is defined as an economic side effect of cancer treatment.^{2,8} It describes the financial burden experienced by cancer survivors with high out-of-pocket medical payments. “Financial burden” and “financial distress” are terms commonly used interchangeably with FT.^{9,10} Financial toxicity, first mentioned in 2011, gained traction as a significant impact of cancer treatment in the age of precision medicine.¹¹ In this systematic review, we used the definition proposed by Witte et al., which described FT as “the patient-reported outcome measure (PROM) of perceived subjective financial distress resulting from objective financial burden”.¹⁰ A number of studies highlighted the prevalence of FT for cancer survivors in various contexts globally.^{9,10,12-15} Azzani et al. found that 14.8% to 78.8% of cancer survivors experienced FT, especially in low-income populations.¹² Altice’s systematic review revealed that in the US, the mean annual economic costs of cancer treatment ranged from US\$ 380 to US\$ 8236 and that 12% to 62% of survivors were in debt.¹⁴

Azzani et al., Gordon et al., and Altice et al. reviewed the measures of FT and categorized them as monetary measures, objective measures, and subjective measures.^{9,12,14} The majority of current studies used monetary and objective indicators to describe cancer survivors’ experience with FT. Previous studies on FT suggested that FT, which is related to financial distress, should be measured using patient-reported outcomes. A few cancer-specific and generic PROMs are widely used to evaluate cancer survivors’ FT. Among all measures, the Comprehensive Score for financial Toxicity (COST) was the most commonly used PROM and was developed and validated by de Souza and colleagues in

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4 87 2014.¹⁶ The COST measure demonstrated high internal consistency (Cronbach's $\alpha=0.92$) and high
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6 88 test-retest reliability (ICC=0.80 [0.57-0.92]). Other PROMs included the Breast Cancer Finances
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8 89 Survey Inventory (BCFS),¹⁷ Socioeconomic Wellbeing scale (SWBS),¹⁸ and InCharge Financial
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10 90 Distress/Financial Wellbeing Scale (InCharge).¹⁹ Additionally, validated subscales, such as Social
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12 91 Difficulties Inventory Cancer Care Outcomes (SDI) and the Research and Surveillance Consortium
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14 92 Patient survey (CanCPRS), were also used to evaluate FT.^{20,21} However, the development and
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16 93 validation of current PROMs varied significantly, and none of them are considered the gold standard.

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19 95 In accordance with our definition of FT, Witte et al. summarized methods for measuring
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21 96 subjective financial distress in cancer survivors.¹⁰ However, they did not report the psychometric
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23 97 properties of PROMs, making it hard for researchers to choose one measure from the existing PROMs
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25 98 to assess FT. Since accurate and reproducible PROMs are a prerequisite for robust results, choosing an
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27 99 acceptable PROM with strong psychometric properties is essential.^{22,23} However, a description of the
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29 100 psychometric properties of existing PROMs is still lacking.

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33 102 Therefore, to obtain robust evidence and enable a better understanding of the psychometric
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35 103 properties of PROMs assessing FT for cancer survivors, our study adopted the CONsensus-based
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37 104 Standards for the selection of health Measurement INstruments (COSMIN) approach to
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39 105 comprehensively report psychometric properties from multiple validation studies.²⁴ As a method for
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41 106 selecting PROMs both in research and in clinical practice, this approach is used for the first time to
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43 107 focus on the various psychometric properties of the validation studies rather than reporting the content
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45 108 of PROMs.

109 110 **METHODS AND ANALYSIS**

111 **Aim and design**

112 The aim of this study is to apply COSMIN methodology to systematically review the content and
113 structural validity of PROMs measuring FT for cancer survivors.²⁴ This systematic review will be
114 conducted according to the guidance of COSMIN and the Preferred Reporting Items for Systematic
115 Reviews and Meta-Analyses statement (PRISMA).²⁵

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117 Search strategy

118 The comprehensive search strategy will be developed in conjunction with a senior health research
119 librarian. A comprehensive three-step search of published studies will be undertaken. The first step will
120 involve a limited search via PubMed/MEDLINE to capture keywords by analyzing the text in the title
121 and abstract and the index terms used to describe each paper. This will inform the development of a
122 search strategy specific to each database, which will be the second step. Finally, references in all
123 included studies will be manually reviewed to supplement the database search.

124

125 Papers will be collected from the following databases: PubMed/MEDLINE, MEDLINE (Ovid),
126 EMBASE (Ovid), CINAHL (EBSCO), PsycINFO (EBSCO), Web of Science, ProQuest Dissertations
127 and Theses, and Cochrane Library (Wiley). In PubMed/Medline, we will search for papers in English
128 using MeSH terms ([cancer OR neoplasms] AND ["cancer survivors" OR patient OR survivors] AND
129 "cost of illness") combined with (cancer OR [patient* OR survivor*] AND [cost OR bill* OR expense
130 OR productivity loss OR "out-of-pocket" OR "economic burden" OR "financial toxicity" OR
131 "financial hardship" OR "financial burden"] AND "COSMIN search filter"). A COSMIN search filter
132 was developed instead of using keywords, such as questionnaire, survey, and scale, to find studies on
133 measurement properties. The search strategies are presented in Supplementary file I. Finally, references
134 in all included studies will be manually reviewed to supplement the database search.

135

136 Inclusion and exclusion criteria

137 The inclusion criteria are as follows: 1) studies that focus on individuals with any type of cancer
138 who are still living;²⁶ 2) studies that aim to assess the FT (or financial hardship, financial distress, or
139 financial burden) of cancer survivors, which is related to the economic side effects of cancer treatment,
140 by using PROMs; 3) studies that evaluate one or more measurement proprieties of a PROM, including
141 but not limited to structural validity, internal consistency, reliability, measurement error, hypothesis
142 testing for construct validity, cross-cultural validity/measurement invariance, criterion validity, and
143 responsiveness; and 4) studies published in English. Original studies in any country or setting and with
144 any sample size are eligible for inclusion. Studies that provide indirect evidence of the measurement

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4 145 properties (e.g., using the PROM to compare with another instrument) are excluded.

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8 147 **Study screening and selection**

9 148 All identified citations will be imported into Endnote X8 (Clarivate Analytics, PA, USA). After
10
11 149 removal of duplicates, two reviewers will independently perform the screening and selection (ZZ &
12
13 150 WX) based on the established inclusion and exclusion criteria. Any disagreements that arise between
14
15 151 the two reviewers will be resolved by a third reviewer (YH).

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19 153 **Quality appraisal**

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21 154 The measurement properties will be evaluated in three steps. First, we will apply the COSMIN
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23 155 Risk of Bias Checklist to assess the methodological quality of PROM development. This domain
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25 156 contains 35 items grouped into two sections: PROM design and cognitive interview studies. Second,
26
27 157 we will assess the methodological quality in terms of content validity. This section includes 38 items
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29 158 divided into patient and professional sections that ask about the relevance, comprehensiveness, and
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31 159 comprehensibility of the PROM. Finally, we will evaluate eight measurement properties: structural
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33 160 validity, internal consistency, cross-cultural validity, reliability, measurement error, criterion validity,
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35 161 hypothesis testing, and responsiveness. Each measurement property will be rated as “very good”,
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37 162 “adequate”, “doubtful” or “inadequate quality”. The methodological quality of the study will be rated
38
39 163 based on the worst score counts method. For example, if any items of the domain are scored as
40
41 164 “inadequate quality”, the overall quality of the study will be rated as “inadequate quality”. Two
42
43 165 reviewers (ZZ & WX) will independently appraise the studies, and disagreements will be resolved by a
44
45 166 third reviewer (YH).

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49 168 **Data extraction**

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51 169 Two reviewers (ZZ & WX) will independently extract data from the included papers, including
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53 170 the authors, date of publication, PROM, country/language, study design, study population, sample size,
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55 171 measurement domains, number of items, and main findings. Additionally, data from the COSMIN
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57 172 Checklist will be extracted. Any discrepancies will be resolved through discussion between the two
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59 173 reviewers.

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175 Data synthesis

176 Data synthesis will comprise two steps. First, the results of the single study will be rated against
177 the updated criteria for good measurement properties, including structural validity, internal
178 consistency, reliability, measurement error, hypothesis testing for construct validity, cross-cultural
179 validity/measurement invariance, criterion validity, and responsiveness. Each measurement property
180 will be rated as sufficient (+), insufficient (-), or indeterminate (?). If the ratings for each study are all
181 sufficient or insufficient, the results can be pooled, and the overall rating will be either sufficient or
182 insufficient. If the ratings are inconsistent, explanations of inconsistency will be explored. If the
183 explanation is reasonable, ratings will be provided in the subgroup (e.g., different languages of a
184 PROM); however, if the explanation is not reasonable, the overall rating of this measurement property
185 will be inconsistent (\pm). If there is no information supporting the rating, the overall rating will be
186 indeterminate (?). Consequently, the evidence will be summarized and graded according to the
187 modified GRADE system (e.g., high, medium, low, and very low evidence). Four of the five GRADE
188 factors have been adopted in the COSMIN methodology, including risk of bias, inconsistency,
189 imprecision, and indirectness. The quality of the evidence is graded for each measurement property and
190 each PROM separately. Two reviewers will independently assess the quality of the evidence with
191 GRADE, and any discrepancies will be resolved by a third reviewer (YH).

192

193 Patient and public involvement

194 No patients or members of the public were involved in the design of this systematic review.

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196 Ethics and dissemination

197 No individual data are involved in this systematic review. The results will be disseminated to a
198 clinical audience and policy makers through peer-reviewed journals and conferences and will support
199 researchers in choosing the best measure to evaluate the FT of cancer survivors.

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DISCUSSION

202 To our knowledge, this is the first systematic review that will identify generic and cancer-specific

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4 203 PROMs to assess FT for cancer survivors and provide a comprehensive picture of their measurement
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6 204 properties. The synthesized results will allow healthcare professionals and policy-makers to choose a
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8 205 validated PROM based on its psychometric properties. This study will also enable guideline developers
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10 206 to better understand the underlying measurement properties of existing PROMs measuring FT for
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12 207 cancer survivors.

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15 209 While we will develop a systematic review based on the COSMIN criteria and PRISMA
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17 210 guidelines, some potential challenges may exist. First, according to the COSMIN criteria, nine
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19 211 psychometric properties should be assessed: content validity, structural validity, internal consistency,
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21 212 reliability, measurement error, hypothesis testing for construct validity, cross-cultural
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23 213 validity/measurement invariance, criterion validity, and responsiveness. However, the included studies
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25 214 may report only a of these different psychometric properties. Our conclusion may therefore apply only
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27 215 to specific properties of PROMs. Second, the discordant use of FT leads to a very large variety of
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29 216 scales and questionnaires used to measure this issue. Among them, many studies used self-made
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31 217 questionnaires and did not provide enough information on validation. Therefore, we will include only
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33 218 studies that aimed to develop or validate a PROM. Last, potential publication bias may still exist, as
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35 219 with all systematic reviews. We will extensively search multiple electronic databases without time
36
37 220 restrictions to minimize the likelihood of missing relevant studies.

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40 222 This review will be the first to evaluate the psychometric properties of FT measures for cancer
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42 223 survivors. The results of the present systematic review will provide a foundation for future studies
43
44 224 assessing FT. We will publish this study in a peer-reviewed academic journal to reach both academic
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46 225 and non-academic audiences interested in the topic. We will also present the results at both national and
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48 226 international conferences. A summary of the results will be presented to healthcare professionals and
49
50 227 health consumer groups. In addition, policy-makers will be reached via briefing notes and other potential
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52 228 avenues.

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58 231 None

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5 233 **Contributors**

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7 234 Study design: ZZ; study screening and selection: ZZ, WX, YH; quality appraisal: ZZ, WX, YH;

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9 235 data extraction: ZZ, WX; data analysis: ZZ, WX, YH; supervision: LY, YH, JP; protocol and

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25 243 **Competing interests**

26
27 244 None declared

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1 **Supplementary file I Search strategy for PubMed/Medline**

Search	Query
#1	Cancer[Title/Abstract] OR neoplasms[MeSH]
#2	Patient?[Title/Abstract] OR survivor?[Title/Abstract] OR patients[MeSH] OR “cancer survivors”[MeSH] OR survivors[MeSH]
#3	Cost[Title/Abstract] OR bill?[Title/Abstract] OR expense[Title/Abstract] OR “productivity loss”[Title/Abstract] OR “out-of-pocket”[Title/Abstract] OR “economic burden”[Title/Abstract] OR “financial toxicity”[Title/Abstract] OR “financial hardship”[Title/Abstract] OR “financial burden”[Title/Abstract] OR “financial effect”[Title/Abstract] OR “financial stress”[Title/Abstract] OR “economic burden”[Title/Abstract] OR “economic hardship”[Title/Abstract] OR “co-payment”[Title/Abstract])) OR “cost of illness”[MeSH]
#4	Scale?[Title/Abstract] OR “patient reported outcome measur*”[Title/Abstract] OR PROM? [Title/Abstract] OR measure* [Title/Abstract] OR “Patient Reported Outcome Measures*”[MeSH] OR “Surveys and Questionnaires”[MeSH]
#5	(instrumentation[sh] OR methods[sh] OR “Validation Studies”[pt] OR “Comparative Study”[pt] OR “psychometrics”[MeSH] OR psychometr*[tiab] OR clinimetr*[tw] OR clinometr*[tw] OR “outcome assessment (health care)”[MeSH] OR “outcome assessment”[tiab] OR “outcome measure*”[tw] OR “observer variation”[MeSH] OR “observer variation”[tiab] OR “Health Status Indicators”[Mesh] OR “reproducibility of results”[MeSH] OR reproducib*[tiab] OR “discriminant analysis”[MeSH] OR reliab*[tiab] OR unreliab*[tiab] OR valid*[tiab] OR “coefficient of variation”[tiab] OR coefficient[tiab] OR homogeneity[tiab] OR homogeneous[tiab] OR “internal consistency”[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR (item[tiab] AND (correlation*[tiab] OR selection*[tiab] OR reduction*[tiab])) OR agreement[tw] OR precision[tw] OR imprecision[tw] OR “precise values”[tw] OR test-retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intra-observer[tiab] OR intertechnician[tiab] OR inter-technician[tiab] OR intratechnician[tiab] OR intra-technician[tiab] OR interexaminer[tiab] OR inter-examiner[tiab] OR intraexaminer[tiab] OR intra-examiner[tiab] OR interassay[tiab] OR inter-assay[tiab] OR intraassay[tiab] OR intra-assay[tiab] OR interindividual[tiab] OR inter-individual[tiab] OR intraindividual[tiab] OR intra-individual[tiab] OR interparticipant[tiab] OR inter-

	<p>participant[tiab] OR intraparticipant[tiab] OR intra-participant[tiab] OR kappa[tiab] OR kappa's[tiab] OR kappas[tiab] OR repeatab*[tw] OR ((replicab*[tw] OR repeated[tw]) AND (measure[tw] OR measures[tw] OR findings[tw] OR result[tw] OR results[tw] OR test[tw] OR tests[tw])) OR generaliza*[tiab] OR generalisa*[tiab] OR concordance[tiab] OR (intraclass[tiab] AND correlation*[tiab]) OR discriminative[tiab] OR "known group"[tiab] OR "factor analysis"[tiab] OR "factor analyses"[tiab] OR "factor structure"[tiab] OR "factor structures"[tiab] OR dimension*[tiab] OR subscale*[tiab] OR (multitrait[tiab] AND scaling[tiab] AND (analysis[tiab] OR analyses[tiab])) OR "item discriminant"[tiab] OR "interscale correlation*" [tiab] OR error[tiab] OR errors[tiab] OR "individual variability"[tiab] OR "interval variability"[tiab] OR "rate variability"[tiab] OR (variability[tiab] AND (analysis[tiab] OR values[tiab])) OR (uncertainty[tiab] AND (measurement[tiab] OR measuring[tiab])) OR "standard error of measurement"[tiab] OR sensitiv*[tiab] OR responsive*[tiab] OR (limit[tiab] AND detection[tiab]) OR "minimal detectable concentration"[tiab] OR interpretab*[tiab] OR ((minimal[tiab] OR minimally[tiab] OR clinical[tiab] OR clinically[tiab]) AND (important[tiab] OR significant[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR (small*[tiab] AND (real[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR "meaningful change"[tiab] OR "ceiling effect"[tiab] OR "floor effect"[tiab] OR "Item response model"[tiab] OR IRT[tiab] OR Rasch[tiab] OR "Differential item functioning"[tiab] OR DIF[tiab] OR "computer adaptive testing"[tiab] OR "item bank"[tiab] OR "cross-cultural equivalence"[tiab])</p>
#6	<p>("addresses"[Publication Type] OR "biography"[Publication Type] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])</p>
#7	#1 AND #2 AND #3 AND #4 AND #5
#8	#7 NOT #6

Supplementary file for editor only: PRISMA-P 2015 Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	√		P2, line 20-21
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		√	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract		√	
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	√		P1, line 4-18
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	√		P10, line 233-237
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		√	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	√		P10, line 239-241
Sponsor	5b	Provide name for the review funder and/or sponsor	√		P10, line 239-241
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		√	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	√		P4-P5, line 80-93
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	√		P5, 102-103
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	√		P6-P7, line 136-145
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	√		P6, line 125-127
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated	√		P6, line 127-133 + Supplementary file I

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	√		P7, line 148
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	√		P7, line 139-151
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	√		P7, line 169-173
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any preplanned data assumptions and simplifications	√		P7, line 169-173
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	√		P8, line 176-179
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	√		P7, line 153-166
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized		√	NA
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)		√	NA
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)		√	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	√		P8, line 175-191
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)		√	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	√		P8, line 186-191

BMJ Open

Psychometric properties of self-reported financial toxicity measures in cancer survivors: a systematic review protocol using COSMIN methodology

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-036365.R1
Article Type:	Protocol
Date Submitted by the Author:	17-Mar-2020
Complete List of Authors:	Zhu, Zheng; Fudan University School of Nursing, Xing, Weijie; Fudan University School of Nursing, Lizarondo, Lucylynn; University of Adelaide, The Joanna Briggs Institute Peng, Jian; Fudan University School of Nursing Hu, Yan; Fudan University, School of Nursing So, WK; The Chinese University of Hong Kong
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Health economics, Health services research
Keywords:	ONCOLOGY, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, HEALTH ECONOMICS

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4 1 **Psychometric properties of self-reported financial toxicity measures in cancer**
5 2 **survivors: a systematic review protocol using COSMIN methodology**
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4 20 **Psychometric properties of self-reported financial toxicity measures in cancer**
5 21 **survivors: a systematic review protocol using COSMIN methodology**
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11 23 **Abstract**

12 24 **Introduction:** Due to the higher costs associated with advancements in cancer treatment and
13 25 longer duration of cancer survivorship, increasing financial toxicity has become a great threat to
14 26 survivors, caregivers, and public healthcare systems. Since accurate and reproducible measures are
15 27 prerequisites for robust results, choosing an acceptable measure with strong psychometric properties to
16 28 assess financial toxicity is essential. However, a description of the psychometric properties of existing
17 29 measures is still lacking. The aim of this study is to apply COnsensus-based Standards for the selection
18 30 of health Measurement INstruments (COSMIN) methodology to systematically review the content and
19 31 structural validity of patient-reported outcome measures (PROMs) of financial toxicity for cancer
20 32 survivors.
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34 34 **Methods and analysis:** PubMed/MEDLINE, MEDLINE (Ovid), EMBASE (Ovid), CINAHL
35 35 (EBSCO), Web of Science, ProQuest Dissertations and Theses, and Cochrane Library (Wiley) will be
36 36 comprehensively searched from database inception to November 15, 2019. Studies that report the
37 37 measurement properties of PROMs assessing financial toxicity for cancer survivors will be included.
38 38 The evaluation of measurement properties, data extraction, and data synthesis will be conducted
39 39 according to the COSMIN methodology.
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41 41 **Ethics and dissemination:** No individual data are involved in this systematic review. The results
42 42 will be disseminated to a clinical audience and policy makers through peer-reviewed journals and
43 43 conferences and will support researchers in choosing the best measure to evaluate the financial toxicity
44 44 of cancer survivors.
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46 46 **Keywords:** cancer; oncology; financial toxicity; systematic review; COSMIN; PROM

48 48 **Word count:** 2030

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4 50 **Strengths and limitations of this study**

- 5 51 ● This is the first systematic review that will identify generic and cancer-specific patient-reported
6
7 52 outcome measures (PROMs) to assess FT for cancer survivors and provide a comprehensive
8
9 53 picture of their measurement properties.
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11 54 ● A robust three-step search of published studies will be undertaken to capture a large range of
12
13 55 papers.
14
15 56 ● COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN)
16
17 57 approach will be followed to comprehensively report psychometric properties from multiple
18
19 58 validation studies.
20
21 59 ● The COSMIN approach will allow healthcare professionals and policy-makers to choose a
22
23 60 validated PROM based on its psychometric properties.
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25 61 ● This systematic review will only include studies published in English which may bias the results
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27 62 against non-English speaking countries.
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64 INTRODUCTION

65 Given the higher costs associated with advancements in cancer treatment and longer duration of
66 cancer survivorship, the increasing financial burden is currently becoming a great threat to survivors,
67 caregivers, and public healthcare systems.^{1,2} The total global spending on cancer care medicines
68 increased from US\$ 96 billion in 2013 to US\$ 133 billion in 2017 at a compound annual growth rate of
69 6.5%, which is almost two times larger than the global GDP growth rate.^{3,4} Cancer treatment and
70 survivorship are estimated to cost US\$ 173 billion in 2020.⁵ Notably, middle-income and low-income
71 countries relying on out-of-pocket payments contribute to global disparities in healthcare spending and
72 inequity in financial vulnerability for cancer survivors.^{6,7}

73
74 The term “financial toxicity” (FT) is defined as an economic side effect of cancer treatment.^{2,8} It
75 describes the financial burden experienced by cancer survivors with high out-of-pocket medical
76 payments. “Financial burden” and “financial distress” are terms commonly used interchangeably with
77 FT.^{9,10} Financial toxicity, first mentioned in 2011, gained traction as a significant impact of cancer
78 treatment in the age of precision medicine.¹¹ FT covers both “objective financial burden” and
79 “subjective financial distress”. The objective financial burden is directly due to the cost of cancer
80 treatment which increases over time. Subjective financial distress captures all negative emotions,
81 uncomfortable experience and psychological stress of cancer survivors resulting from objective
82 financial burden^{9,11}.

83
84 A number of studies highlighted the prevalence of FT for cancer survivors in various contexts
85 globally.^{9,10,12-15} Azzani et al. found that 14.8% to 78.8% of cancer survivors experienced FT,
86 especially in low-income populations.¹² Altice’s systematic review revealed that in the US, the mean
87 annual economic costs of cancer treatment ranged from US\$ 380 to US\$ 8236 and that 12% to 62% of
88 survivors were in debt.¹⁴

89
90 Azzani et al., Gordon et al., and Altice et al. reviewed the measures of FT and categorized them as
91 monetary measures, objective measures, and subjective measures.^{9,12,14} The majority of current studies
92 used monetary and objective indicators to describe cancer survivors’ experience with FT. Previous

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4 93 studies suggested that FT should be measured using patient-reported outcomes to reflect cancer
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6 94 survivors' thoughts, complaints, and opinions that any numbers or observers can't.¹⁰ The financial
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8 95 burden of cancer and its treatment needs to be understood within the context of the patient's personal
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10 96 experiences and circumstances. A few cancer-specific and generic PROMs are widely used to evaluate
11
12 97 cancer survivors' FT. Among all measures, the Comprehensive Score for financial Toxicity (COST)
13
14 98 was the most commonly used PROM and was developed and validated by de Souza and colleagues in
15
16 99 2014.¹⁶ The COST measure demonstrated high internal consistency (Cronbach's $\alpha=0.92$) and high
17
18 100 test-retest reliability (ICC=0.80 [0.57-0.92]). Other PROMs included the Breast Cancer Finances
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20 101 Survey Inventory (BCFS),¹⁷ Socioeconomic Wellbeing scale (SWBS),¹⁸ and InCharge Financial
21
22 102 Distress/Financial Wellbeing Scale (InCharge).¹⁹ Additionally, validated subscales, such as Social
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24 103 Difficulties Inventory Cancer Care Outcomes (SDI) and the Research and Surveillance Consortium
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26 104 Patient survey (CanCPRS), were also used to evaluate FT.^{20, 21} However, the development and
27
28 105 validation of current PROMs varied significantly, and none of them are considered the gold standard.
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30 106

31 107 In accordance with our definition of FT, Witte et al. summarized methods for measuring
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33 108 subjective financial distress in cancer survivors.¹⁰ However, they did not report the psychometric
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35 109 properties of PROMs, making it hard for researchers to choose one measure from the existing PROMs
36
37 110 to assess FT. Since accurate and reproducible PROMs are a prerequisite for robust results, choosing an
38
39 111 acceptable PROM with strong psychometric properties is essential.^{22,23} However, a description of the
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41 112 psychometric properties of existing PROMs is still lacking.
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44 114 Therefore, to obtain robust evidence and enable a better understanding of the psychometric
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46 115 properties of PROMs assessing FT for cancer survivors, our study adopted the COnsensus-based
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48 116 Standards for the selection of health Measurement INstruments (COSMIN) approach to
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50 117 comprehensively report psychometric properties from multiple validation studies.²⁴ As a method for
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52 118 selecting PROMs both in research and in clinical practice, this approach is used for the first time to
53
54 119 focus on the various psychometric properties of the validation studies rather than reporting the content
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56 120 of PROMs.
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58 121

122 **METHODS AND ANALYSIS**

123 **Aim and design**

124 The aim of this study is to apply COSMIN methodology to systematically review the content and
125 structural validity of PROMs measuring FT for cancer survivors.²⁴ This systematic review will be
126 conducted according to the guidance of COSMIN and the Preferred Reporting Items for Systematic
127 Reviews and Meta-Analyses statement (PRISMA).²⁵

129 **Search strategy**

130 The comprehensive search strategy will be developed in conjunction with a senior health research
131 librarian. A comprehensive three-step search of published studies will be undertaken. The first step will
132 involve a limited search via PubMed/MEDLINE to capture keywords by analyzing the text in the title
133 and abstract and the index terms used to describe each paper. This will inform the development of a
134 search strategy specific to each database, which will be the second step. Finally, references in all
135 included studies will be manually reviewed to supplement the database search.

136
137 Papers will be collected from the following databases from inception to 1st March 2020:
138 PubMed/MEDLINE, MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO), PsycINFO (EBSCO),
139 Web of Science, ProQuest Dissertations and Theses, and Cochrane Library (Wiley). In
140 PubMed/Medline, we will search for papers in English using MeSH terms ([cancer OR neoplasms]
141 AND [“cancer survivors” OR patient OR survivors] AND “cost of illness”) combined with (cancer OR
142 [patient* OR survivor*] AND [cost OR bill* OR expense OR productivity loss OR “out-of-pocket” OR
143 “economic burden” OR “financial toxicity” OR “financial hardship” OR “financial burden”] AND
144 “COSMIN search filter”). A COSMIN search filter was developed instead of using keywords, such as
145 questionnaire, survey, and scale, to find studies on measurement properties. The search strategies are
146 presented in Supplementary file I. Finally, references in all included studies will be manually reviewed
147 to supplement the database search.

149 **Inclusion and exclusion criteria**

150 The inclusion criteria are as follows: 1) studies that focus on individuals with any type of cancer

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4 151 who are still living;²⁶ 2) studies that aim to assess the FT (or financial hardship, financial distress, or
5
6 152 financial burden) of cancer survivors, which is related to the economic side effects of cancer treatment,
7
8 153 by using PROMs; 3) studies that evaluate one or more measurement proprieties of a PROM, including
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10 154 but not limited to structural validity, internal consistency, reliability, measurement error, hypothesis
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12 155 testing for construct validity, cross-cultural validity/measurement invariance, criterion validity, and
13
14 156 responsiveness; and 4) studies published in English. Original studies in any country or setting and with
15
16 157 any sample size are eligible for inclusion. Studies that provide indirect evidence of the measurement
17
18 158 properties (e.g., using the PROM to compare with another instrument) are excluded.

19 159

20 160 **Study screening and selection**

21 161 All identified citations will be imported into Endnote X8 (Clarivate Analytics, PA, USA). After
22
23 162 removal of duplicates, two reviewers will independently perform the screening and selection (ZZ &
24
25 163 WX) based on the established inclusion and exclusion criteria. Any disagreements that arise between
26
27 164 the two reviewers will be resolved by a third reviewer (YH).

28 165

29 166 **Quality appraisal**

30 167 The measurement properties will be evaluated in three steps. First, we will apply the COSMIN
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32 168 Risk of Bias Checklist to assess the methodological quality of PROM development. This domain
33
34 169 contains 35 items grouped into two sections: PROM design and cognitive interview studies. Second,
35
36 170 we will assess the methodological quality in terms of content validity. This section includes 38 items
37
38 171 divided into patient and professional sections that ask about the relevance, comprehensiveness, and
39
40 172 comprehensibility of the PROM. Finally, we will evaluate eight measurement properties: structural
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42 173 validity, internal consistency, cross-cultural validity, reliability, measurement error, criterion validity,
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44 174 hypothesis testing, and responsiveness. Each measurement property will be rated as “very good”,
45
46 175 “adequate”, “doubtful” or “inadequate quality”. The methodological quality of the study will be rated
47
48 176 based on the worst score counts method. For example, if any items of the domain are scored as
49
50 177 “inadequate quality”, the overall quality of the study will be rated as “inadequate quality”. Two
51
52 178 reviewers (ZZ & WX) will independently appraise the studies, and disagreements will be resolved by a
53
54 179 third reviewer (YH).

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181 Data extraction

182 Two reviewers (ZZ & WX) will independently extract data from the included papers, including
183 the authors, date of publication, PROM, country/language, study design, study population, sample size,
184 measurement domains, number of items, and main findings. Additionally, data from the COSMIN
185 Checklist will be extracted. Any discrepancies will be resolved through discussion between the two
186 reviewers.

187

188 Data synthesis

189 Data synthesis will comprise two steps. First, the results of the single study will be rated against
190 the updated criteria for good measurement properties, including structural validity, internal
191 consistency, reliability, measurement error, hypothesis testing for construct validity, cross-cultural
192 validity/measurement invariance, criterion validity, and responsiveness. Each measurement property
193 will be rated as sufficient (+), insufficient (-), or indeterminate (?). If the ratings for each study are all
194 sufficient or insufficient, the results can be pooled, and the overall rating will be either sufficient or
195 insufficient. If the ratings are inconsistent, explanations of inconsistency will be explored. If the
196 explanation is reasonable, ratings will be provided in the subgroup (e.g., different languages of a
197 PROM); however, if the explanation is not reasonable, the overall rating of this measurement property
198 will be inconsistent (\pm). If there is no information supporting the rating, the overall rating will be
199 indeterminate (?). Consequently, the evidence will be summarized and graded according to the
200 modified GRADE system (e.g., high, medium, low, and very low evidence). Four of the five GRADE
201 factors have been adopted in the COSMIN methodology, including risk of bias, inconsistency,
202 imprecision, and indirectness. The quality of the evidence is graded for each measurement property and
203 each PROM separately. Two reviewers will independently assess the quality of the evidence with
204 GRADE, and any discrepancies will be resolved by a third reviewer (YH).

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206 Patient and public involvement

207 No patients or members of the public were involved in the design of this systematic review.

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4 209 **Ethics and dissemination**

5 210 No individual data are involved in this systematic review. The results will be disseminated to a
6
7 211 clinical audience and policy makers through peer-reviewed journals and conferences and will support
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9 212 researchers in choosing the best measure to evaluate the FT of cancer survivors.
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11 213

12
13 214 **DISCUSSION**

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15 215 To our knowledge, this is the first systematic review that will identify generic and cancer-specific
16
17 216 PROMs to assess FT for cancer survivors and provide a comprehensive picture of their measurement
18
19 217 properties. The synthesized results will allow healthcare professionals and policy-makers to choose a
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21 218 validated PROM based on its psychometric properties. This study will also enable guideline developers
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23 219 to better understand the underlying measurement properties of existing PROMs measuring FT for
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25 220 cancer survivors.
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29 222 While we will develop a systematic review based on the COSMIN criteria and PRISMA
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31 223 guidelines, some potential challenges may exist. First, according to the COSMIN criteria, nine
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33 224 psychometric properties should be assessed: content validity, structural validity, internal consistency,
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35 225 reliability, measurement error, hypothesis testing for construct validity, cross-cultural
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37 226 validity/measurement invariance, criterion validity, and responsiveness. However, the included studies
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39 227 may report only some of these psychometric properties. Our conclusion may therefore apply only to
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41 228 specific properties of PROMs. Second, the discordant use of FT leads to a very large variety of scales
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43 229 and questionnaires used to measure this issue. Among them, many studies used self-made
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45 230 questionnaires and did not provide enough information on validation. Therefore, we will include only
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47 231 studies that aimed to develop or validate a PROM. Last, potential publication bias may still exist, as
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49 232 with all systematic reviews. We will extensively search multiple electronic databases without time
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51 233 restrictions to minimize the likelihood of missing relevant studies. Despite the challenges, based on our
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53 234 preliminary search, it will be highly possible to draw valid conclusions on the content and structural
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55 235 validity of PROMs measuring FT for cancer survivors.
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58 237 This review will be the first to evaluate the psychometric properties of FT measures for cancer
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238 survivors. The results of the present systematic review will provide a foundation for future studies
239 assessing FT. We will publish this study in a peer-reviewed academic journal to reach both academic
240 and non-academic audiences interested in the topic. We will also present the results at both national
241 and international conferences. A summary of the results will be presented to healthcare professionals
242 and health consumer groups. In addition, policy-makers will be reached via briefing notes and other
243 potential avenues.

244

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246 None

247

248 **Contributors**

249 Study design: ZZ; study screening and selection: ZZ, WX, YH; quality appraisal: ZZ, WX, YH;
250 data extraction: ZZ, WX; data analysis: ZZ, WX, YH; supervision: LY, YH, JP; protocol and
251 manuscript writing: ZZ, WX; critical revisions: LY, YH, WS. All authors revised and accepted the
252 final draft.

253

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257

258 **Competing interests**

259 None declared

260

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1 **Supplementary file I Search strategy for PubMed/Medline**

Search	Query
#1	Cancer[Title/Abstract] OR neoplasms[MeSH]
#2	Patient?[Title/Abstract] OR survivor?[Title/Abstract] OR patients[MeSH] OR “cancer survivors”[MeSH] OR survivors[MeSH]
#3	Cost[Title/Abstract] OR bill?[Title/Abstract] OR expense[Title/Abstract] OR “productivity loss”[Title/Abstract] OR “out-of-pocket”[Title/Abstract] OR “economic burden”[Title/Abstract] OR “financial toxicity”[Title/Abstract] OR “financial hardship”[Title/Abstract] OR “financial burden”[Title/Abstract] OR “financial effect”[Title/Abstract] OR “financial stress”[Title/Abstract] OR “economic burden”[Title/Abstract] OR “economic hardship”[Title/Abstract] OR “co-payment”[Title/Abstract])) OR “cost of illness”[MeSH]
#4	Scale?[Title/Abstract] OR “patient reported outcome measur*”[Title/Abstract] OR PROM? [Title/Abstract] OR measure* [Title/Abstract] OR “Patient Reported Outcome Measures*”[MeSH] OR “Surveys and Questionnaires”[MeSH]
#5	(instrumentation[sh] OR methods[sh] OR “Validation Studies”[pt] OR “Comparative Study”[pt] OR “psychometrics”[MeSH] OR psychometr*[tiab] OR clinimetr*[tw] OR clinometr*[tw] OR “outcome assessment (health care)”[MeSH] OR “outcome assessment”[tiab] OR “outcome measure*”[tw] OR “observer variation”[MeSH] OR “observer variation”[tiab] OR “Health Status Indicators”[Mesh] OR “reproducibility of results”[MeSH] OR reproducib*[tiab] OR “discriminant analysis”[MeSH] OR reliab*[tiab] OR unreliab*[tiab] OR valid*[tiab] OR “coefficient of variation”[tiab] OR coefficient[tiab] OR homogeneity[tiab] OR homogeneous[tiab] OR “internal consistency”[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR (item[tiab] AND (correlation*[tiab] OR selection*[tiab] OR reduction*[tiab])) OR agreement[tw] OR precision[tw] OR imprecision[tw] OR “precise values”[tw] OR test-retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intra-observer[tiab] OR intertechnician[tiab] OR inter-technician[tiab] OR intratechnician[tiab] OR intra-technician[tiab] OR interexaminer[tiab] OR inter-examiner[tiab] OR intraexaminer[tiab] OR intra-examiner[tiab] OR interassay[tiab] OR inter-assay[tiab] OR intraassay[tiab] OR intra-assay[tiab] OR interindividual[tiab] OR inter-individual[tiab] OR intraindividual[tiab] OR intra-individual[tiab] OR interparticipant[tiab] OR inter-

	<p>participant[tiab] OR intraparticipant[tiab] OR intra-participant[tiab] OR kappa[tiab] OR kappa's[tiab] OR kappas[tiab] OR repeatab*[tw] OR ((replicab*[tw] OR repeated[tw]) AND (measure[tw] OR measures[tw] OR findings[tw] OR result[tw] OR results[tw] OR test[tw] OR tests[tw])) OR generaliza*[tiab] OR generalisa*[tiab] OR concordance[tiab] OR (intraclass[tiab] AND correlation*[tiab]) OR discriminative[tiab] OR "known group"[tiab] OR "factor analysis"[tiab] OR "factor analyses"[tiab] OR "factor structure"[tiab] OR "factor structures"[tiab] OR dimension*[tiab] OR subscale*[tiab] OR (multitrait[tiab] AND scaling[tiab] AND (analysis[tiab] OR analyses[tiab])) OR "item discriminant"[tiab] OR "interscale correlation*" [tiab] OR error[tiab] OR errors[tiab] OR "individual variability"[tiab] OR "interval variability"[tiab] OR "rate variability"[tiab] OR (variability[tiab] AND (analysis[tiab] OR values[tiab])) OR (uncertainty[tiab] AND (measurement[tiab] OR measuring[tiab])) OR "standard error of measurement"[tiab] OR sensitiv*[tiab] OR responsive*[tiab] OR (limit[tiab] AND detection[tiab]) OR "minimal detectable concentration"[tiab] OR interpretab*[tiab] OR ((minimal[tiab] OR minimally[tiab] OR clinical[tiab] OR clinically[tiab]) AND (important[tiab] OR significant[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR (small*[tiab] AND (real[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR "meaningful change"[tiab] OR "ceiling effect"[tiab] OR "floor effect"[tiab] OR "Item response model"[tiab] OR IRT[tiab] OR Rasch[tiab] OR "Differential item functioning"[tiab] OR DIF[tiab] OR "computer adaptive testing"[tiab] OR "item bank"[tiab] OR "cross-cultural equivalence"[tiab])</p>
#6	<p>("addresses"[Publication Type] OR "biography"[Publication Type] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])</p>
#7	#1 AND #2 AND #3 AND #4 AND #5
#8	#7 NOT #6

Supplementary file for editor only: PRISMA-P 2015 Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	√		P2, line 20-21
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		√	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract		√	
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	√		P1, line 4-18
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	√		P10, line 248-251
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		√	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	√		P10, line 254-256
Sponsor	5b	Provide name for the review funder and/or sponsor	√		P10, line 254-256
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		√	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	√		P4-P5, line 74-112
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	√		P6, 123-125
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	√		P6-P7, line 150-158
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	√		P6, line 138-139
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits,	√		P6, line 140-144 +

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		such that it could be repeated			Supplementary file I
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	√		P7, line 161
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	√		P7, line 162-164
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	√		P8, line 181-186
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	√		P8, line 181-186
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	√		P8, line 184
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	√		P8, line 189-204
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized		√	NA
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)		√	NA
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)		√	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	√		P8, line 189-204
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)		√	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	√		P8, line 203-204